Physiotherapy for people with progressive multiple sclerosis

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Submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

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February 2018

Acknowledgements

My PhD has been a journey which would simply not have been possible without the Bevan Scholarship from NHS Ayrshire & Arran, or without the participants who took part in my studies.

Many people have accompanied me along this journey that I would like to take this opportunity to thank for their help. First and foremost, I would like to thank my principal supervisors Professor Lorna Paul and Dr Elaine Coulter for their patience and enthusiasm in guiding me, shaping me as a researcher, and encouraging my ideas for projects. I would also like to thank my extended supervisory team of Dr Paul Mattison, Linda Miller and Dr Angus McFadyen. To Dr Mattison for his concise and direct input from a medical perspective. To Linda Miller for the practical advice on running a trial in the NHS. To Dr McFadyen for guiding me in the right direction in statistical analysis. A well timed, "Why are you doing it that way?" sending me straight to my stats books. I would also like to thank the staff of the Douglas Grant Rehabilitation centre for their hospitality in hosting my trial, the endless teasing, and the cups of tea that were shared.

My friends and colleagues in the Nursing and Health Care School in The University of Glasgow have been on this journey with me. It has been fun to share my time with them and see others both before and after me in different stages of their own journey.

Further thanks should go to John Wilson and the staff in the Sports Physiology department for use of their lab equipment and highly coveted freezer space. To Josephine Cooney for her help with the ELISA kits. To Dr Jens Bansi for his input on high intensity interval training, again, a simple, "Be careful how you measure that, there can be traps!" sent me scurrying to my textbooks.

Lastly, I would like to thank my family and my friends, whom, I am assured are all looking forward to seeing me again. To my parents for all their support in life. To my beautiful wife Shona, for her continued patience, understanding, and being the voice of levelled reason. To Ramsay, my son, for bringing me so much joy, making me laugh on a daily basis and reminding me to look at the big picture. It is to Shona and Ramsay that I dedicate this thesis.

A lot has changed during the past three years. As well as completing the research contained in this thesis, I got engaged, got married and now have a son. When I told my supervisors at the start of my third year that Shona was pregnant, they said, “You’re going to have one heck of a year!”

They were right.

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Evan Campbell

Publications and presentations produced from this thesis

Publications

Campbell, E., Coulter, E., Mattison, P., McFadyen, A., Miller, L. & Paul, L. 2015. Physiotherapy rehabilitation for people with progressive Multiple Sclerosis: a systematic review. Archives of Physical Medicine and Rehabilitation, 97, 141-151.e3.

Campbell, E., Coulter, E., Mattison, P., McFadyen, A., Miller, L. & Paul, L. 2017. Access, delivery and perceived efficacy of physiotherapy and use of complementary and alternative therapies by people with progressive multiple sclerosis in the United Kingdom: An online survey. Multiple Sclerosis & Related Disorders, 12, 64-69.

Campbell, E., Coulter, E., Mattison, P., McFadyen, A., Miller, L. & Paul, L. 2017. Access and Use of Clinical Services and Disease-Modifying Therapies by People with Progressive Multiple Sclerosis in the United Kingdom. International Journal of MS Care, 19, 275-282.

Campbell, E., Coulter, E., Paul, L. 2017. High intensity interval training for people with multiple sclerosis: a systematic review. Multiple Sclerosis & Related Disorders. *Currently under review*

Oral presentations

Campbell, E., Coulter, E., Mattison, P., McFadyen, A., Miller, L. & Paul, L. (2017) *Access to services for people with Progressive MS*. MS Society Evidence Meeting, November 2017, London, UK.

Campbell, E., Coulter, E., Mattison, P., McFadyen, A., Miller, L. & Paul, L. (2017) *Access to and use of MS Services by people with progressive MS in the UK: an online survey via the UK MS Register*. MS Frontiers, June 2017 Edinburgh, UK.

Campbell, E., Coulter, E., Mattison, P., McFadyen, A., Miller, L. & Paul, L. (2016) *A UK survey of physiotherapy services for people with progressive MS*. Research in MS mobility special interest group, June 2016, Valens, Switzerland.

Poster presentations

Campbell, E., Coulter, E., Mattison, P., McFadyen, A., Miller, L. & Paul, L. *A comparison of high intensity interval training and continuous moderate intensity training in people with progressive Multiple Sclerosis. A randomised controlled trial*. MS Frontiers, June 2017, Edinburgh, UK.

Campbell, E., Coulter, E., Mattison, P., McFadyen, A., Miller, L. & Paul, L. *Access, use and opinion of physiotherapy services by people with progressive MS in the UK: an online survey*. MS Trust Annual Conference, November 2016, Windsor, UK.

Campbell, E., Coulter, E., Bansi, J., Mattison, P., McFadyen, A., Miller, L. & Paul, L. *Access and use of clinical services and disease modifying therapies by people with progressive Multiple Sclerosis in the UK*. Congress of the European Committee for the Treatment and Research in Multiple Sclerosis, September 2016, London UK.

Abstract

Progressive Multiple Sclerosis (MS) is a degenerative neurological disease with no known cure. The overall aim of the research within this thesis was to investigate physiotherapy, an important part of the care, for people with progressive MS. This was done in three studies. A systematic review of the current literature for the effectiveness of physiotherapy for the rehabilitation of people with progressive MS; an online survey of people with progressive MS assessing levels of access to, and use of, clinical services across the United Kingdom; and a feasibility study of High Intensity Interval Training (HIIT) for people with progressive MS.

The systematic search returned 15 studies, 482 participants in total, which investigated eight different interventions: exercise therapy, multi-disciplinary rehabilitation, functional electrical stimulation, botulinum toxin type A injections and manual stretches, inspiratory muscle training, therapeutic standing, acupuncture and body weight supported treadmill training. All studies, apart from one, produced a positive result, however, only one study was adequately powered. In conclusion, the review found that the evidence was positive for using physiotherapy for rehabilitation in people with progressive MS, but further adequately powered research, is required to strengthen this.

In total 1298 people with progressive MS from across the United Kingdom completed the online survey in August to October 2015. Participants were asked regarding access and use of clinical services, delivery and opinion of physiotherapy, and use of complementary and alternative therapies. Access to MS Specialists was high (95%), as was access to a physiotherapist (87%). Seventy seven percent of physiotherapy was delivered by the National Health Service and 32% were currently receiving physiotherapy for their MS. Physiotherapy was very well perceived by people with progressive MS and the most common interventions received were independent (83%) and supervised exercise (71%). Five percent of respondents were currently using disease modifying therapies and 23% had previously taken them. Almost three quarters (74%) received a regular review but 37% received this review less than annually. It was recommended that service providers make steps to address this gap in service provision.

Finally, eight weeks of twice weekly HIIT sessions were compared to twice weekly sessions of continuous moderate intensity training. Ten out of twelve participants completed the trial. The HIIT intervention was well tolerated with 93% adherence, 100% compliance with protocol and no adverse events. There were three adverse events in the continuous training group and compliance was 79%. In addition, those who received HIIT improved their maximal heart rate and mental processing speed while no changes were found in the continuous training group. A larger, fully powered trial is required to confirm these results.

Overall the studies within this thesis demonstrate that physiotherapy has the potential to be beneficial in the rehabilitation of people with progressive MS, that people with progressive MS are engaging with physiotherapy, and that interventions such as HIIT may provide new avenues for eliciting health benefits from this patient group. However, despite these positive findings, more work is required to strengthen the evidence base and gaps in service provision should be addressed.

(Word count – 66,596)

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List of Abbreviations

BDNF – Brain Derived Neurotrophic Factor

Bpm – beats per minute

BTX-A – Botulinum toxin type A

BWSTT – Body Weight Supported Treadmill Training

CAT – Complementary and Alternative Therapies

CONT – Continuous moderate intensity training

DMTs – Disease modifying Therapies

EDSS – Expanded Disability Status Scale

FES – Functional Electrical Stimulation

FSMC – Fatigue Scale for Motor and Cognitive Function

HADS – Hospital Anxiety and Depression Scale

HDL – High Density Lipoprotein

HIIT – High Intensity Interval Training

HR – Heart Rate

HRMax- Maximal Heart Rate

LDL – Low Density Lipoprotein

MCID – Minimal Clinically Important Difference

MeSH – Medical Subject Headings

MS – Multiple Sclerosis

MSIS-29 – Multiple Sclerosis Impact Scale – 29

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

PEDro – Physiotherapy Evidence Database

PPMS – Primary Progressive Multiple Sclerosis

RCT – Randomised Controlled Trial

RPM – revolutions per minute

SDMT – Symbol digit Modalities Test

SPMS – Secondary Progressive Multiple Sclerosis

TSD – Time Since Diagnosis

UK – United Kingdom

VO_2 max – Maximal uptake of volume of oxygen

VO_2 Peak – Peak uptake of volume of oxygen

Chapter 1 Introduction

Multiple Sclerosis (MS) is a chronic and progressive neurological disease with no known cure (Compston and Coles, 2008). Disease Modifying Therapies (DMTs) are available for people with relapsing remitting MS, but until recently there were no DMTs for people with forms of progressive MS. In November 2017 Ocrelizumab was approved by the European Medicines Agency for use in the early stages of Primary Progressive MS (European Medicines Agency, 2017), however it is not yet available via the National Health Service in the United Kingdom. Due to this and the lack of other available pharmacological treatments, physiotherapy rehabilitation is an important part of the care for people with progressive MS. Access to physiotherapy services is part of the current National Institute for Health Care and Excellence guideline for the management of multiple sclerosis in primary and secondary care (Clinical guideline 186) (NICE, 2014b), and the Healthcare Improvement Scotland Neurological Health Services clinical standards (Healthcare Improvement Scotland, 2009). In addition, the International Progressive MS Alliance, called for more investigation both into the efficacy of physiotherapy in the rehabilitation in people with progressive MS and for more proof of concept studies (Fox et al., 2012).

1.1 Overall aim and investigations central to this thesis

The overall aim of this research was to investigate the use of physiotherapy for people with progressive MS by evaluating the current literature, surveying the patient population in regard to their use of services, and assessing the feasibility of High Intensity Interval Training (HIIT) not previously investigated in this patient group.

1.2 Original contribution of work to knowledge

Each of the studies in this body of work has contributed original knowledge to the current literature of physiotherapy for people with progressive MS. The systematic review was the first to evaluate the evidence for physiotherapy

rehabilitation interventions for people with progressive MS. The online survey also addressed a gap in the literature, as it was the first national exploration of levels of access and use of clinical services by people with progressive MS. Lastly, the exercise trial was the first to explore HIIT in a sample purely of people with progressive MS and an Expanded Disability Status Scale range of 4.0-6.0.

1.3 Organisation of thesis

This thesis comprised three studies. The three studies form a coherent programme of work and complement each other. However, individually the three studies may be of interest to specific audiences including health professionals, academics, service providers and users, third sector organisations and exercise scientists. To help facilitate this two of the studies have already been published, however, this thesis will offer greater detail than presented in the published work.

First, a systematic review was conducted to assess the efficacy of physiotherapy in the rehabilitation of people with progressive MS (Chapter 3). Second, an online survey of people with progressive MS in the United Kingdom (UK) was conducted to investigate the level of access to, delivery of, barriers to access, and opinion of physiotherapy services by people with progressive MS in the UK. Furthermore, the level of access to MS Specialists, a regular review, and use of clinical services was also investigated. Lastly, the use of complementary and alternative therapies was explored (Chapters 4-6). The third study, which was based upon the outcome of the systematic review and the online survey, explored the feasibility of High Intensity Interval Training (HIIT) in people with progressive MS. Furthermore, this study also explored the effects of HIIT, compared to continuous moderate intensity training, on physiological and MS clinical outcomes in people with progressive MS (Chapters 7-8). Overall conclusions and recommendations for each study and the collective body of work are presented in Chapter 9.

Chapter 2 Literature review

This chapter will present the epidemiology of Multiple Sclerosis (MS) and the risk factors for developing MS and progressive MS. It will then outline the different classifications of the disease and the pathophysiology of each, the process of diagnosis and the diagnostic criteria. Different methods of measuring disability in MS will be presented before outlining the clinical signs and symptoms of MS and pharmacological treatments available to people with progressive MS. The effect of MS on employment and the economy will be presented before summarising the effect of MS on mortality and the progression of disability amongst those who have a progressive form of the disease. Multidisciplinary care will then be discussed before outlining research priorities for the field of MS research. Lastly, physiotherapy will be discussed in relation to progressive MS and then the aims and objectives of this thesis will be outlined. An individual justification for each of the three studies undertaken in this PhD will be at the start of chapters 3, 4, and 7.

2.1 Multiple Sclerosis; epidemiology and risk factors for developing MS

Multiple Sclerosis (MS) is a chronic auto-immune inflammatory demyelinating disease with no known cure (Fox et al., 2012). It is the most common cause of neurological disability in young adults and is the predominant member of the group of demyelinating diseases (Compston and Coles, 2008).

It is estimated that approximately 2,300,000 people worldwide have MS with a global prevalence of 33 per 100,000 however incidence, and thus prevalence, varies depending on geographical location (Browne et al., 2014). In the UK there are an estimated 130,000 people with MS and current prevalence is 258.8/100,000 in women and 113.1/100,000 in men, with peak incidence between 40 and 50 years old and peak prevalence between 55 and 60 years old (Mackenzie et al., 2014).

There are many risk factors for developing MS. These include, but are not limited to: gender, age, location, ethnicity, environmental factors and genetics (Compston and Coles, 2008). Incidence is generally higher in women than in men (2:1), apart from cases of primary progressive MS (PPMS) where incidence is relatively equal between genders (Mackenzie et al., 2014). Age at diagnosis is usually between 20 and 40 years (Tullman, 2013).

In general, the prevalence of MS rises with a rise in latitude (Kurtzke, 2005). For example prevalence and incidence rates are the highest in North America with a prevalence rate of 140 per 100,000 compared to the lowest in Sub-Saharan Africa with a rate of 2.1 per 100,000 (Browne et al., 2014).

Historically, the prevalence and incidence of MS in Scotland has been higher than other parts of the UK. This has been documented as far back as the 1950s (Sutherland, 1956) and has been monitored relatively closely (Forbes and Swingler, 1999, Forbes et al., 1999, Grant et al., 1998, Murray et al., 2004, Poskanzer et al., 1980, Rothwell and Charlton, 1998, Shepherd and Downie, 1978, Shepherd and Downie, 1980). Prevalence, especially, has remained high and this has been attributed to an ageing population (Cook et al., 1985, Cook et al., 1988). After the addition of Magnetic Resonance Imaging (MRI) to the diagnostic criteria for MS, the incidence dropped due to the removal of misdiagnosis in some, but not all parts of Scotland, as previously diagnosis was made on clinical presentation alone (Visser et al., 2012).

Even though latitude is a risk factor for developing MS, ethnicity may also be a factor. This is demonstrated in the high incidence and prevalence rate in White Europeans in northern European countries and North America (Browne et al., 2014) in contrast with a low prevalence rate of MS in the Inuit populations of Greenland (Gillie, 2006). In addition to ethnicity, environmental factors also have an influence on risk of developing MS. An increase in prevalence is often seen in first generation migrants if they move to the country in early life (less than ten years old) and in second generation migrants if they move when older (Gale and Martyn, 1995).

Recent opinion to explain disparities in the latitude model propose the concept of the MS ‘genetic burden’ which is a count of all known MS risk alleles that an

individual may carry (Isobe et al., 2013). Furthermore, hereditary factors also increase the risk of developing MS. The risk of developing MS is highest if a person is a monozygotic twin of someone with MS (Hawkes and Macgregor, 2009) and if a child is born of conjugal MS parents (Dyment et al., 2004).

In summary, there is a large body of evidence seeking out the possible cause of MS, however no single locus, environmental factor or infective agent has been identified. Causation is likely cumulative in nature including susceptibility of genes, environmental and hereditary risk factors (Milo and Kahana, 2010).

2.2 Classification of Multiple Sclerosis

There are three main forms of MS: Relapsing Remitting MS (RRMS), Secondary Progressive MS (SPMS), Primary Progressive MS (PPMS) and a rarer form of Progressive Relapsing MS (PRMS) (Lublin and Reingold, 1996). Relapsing remitting MS is characterised by distinct attacks, or relapses, of symptoms with either complete recovery or some neurological deficit. Primary progressive MS is a progression of disability from onset with either continuous progression or with some plateaus and small temporary recovery. Secondary progressive MS is a progressive form of the disease which can follow on from RRMS. Progressive relapsing MS is defined as a steady progression of disability from onset but with distinct relapses with or without complete recovery (Lublin and Reingold, 1996).

It is estimated that, at time of diagnosis, 15% of all cases are PPMS, 5% are PRMS and 80% are RRMS. However, 65% of those who have RRMS will go on to develop SPMS (Mackenzie et al., 2014). Thus 72% of all those who develop MS will enter into a progressive phase of the disease at some point in their life.

In addition to these classifications of MS there is a subcategory of MS called a Clinically Isolated Syndrome (CIS). A CIS is a singular event of demyelination in the central nervous system with symptoms lasting more than 24 hours either at a singular site (mono-focal) or multiple sites (multi-focal) (Miller et al., 2012). Common sites include the spinal cord (transverse myelitis), the optic nerve (optic neuritis) and the brainstem (brainstem syndrome) (Miller et al., 2005).

Many people with a CIS will go on to develop MS with documented development rates varying from 30-75% within 30 years (Miller et al., 2005, Nilsson et al., 2005). The more time that elapses from a CIS the risk of developing MS decreases (Novakova et al., 2014). Indicators for developing MS from a CIS, include a younger age of onset of CIS; oligoclonal bands in the cerebrospinal fluid; a multi-focal attack and a greater number of T2 lesions visible on MRI (Ignacio et al., 2010, Kuhle et al., 2015).

2.3 Pathophysiology

2.3.1 Relapsing remitting Multiple Sclerosis

Relapsing remitting MS is an auto-immune inflammatory demyelinating form of the disease exhibiting remyelination at times, but also over time, axonal loss and the formation of sclerotic plaques from which the disease takes its name (Compston and Coles, 2002). Stages of sclerotic plaque formation include inflammation, demyelination, remyelination, depleted oligodendrocyte numbers and astrocytosis (Compston and Coles, 2008).

An attack, or relapse, is an event of lymphocyte driven inflammation. This follows a leak in the blood brain barrier and the lymphocytes incorrectly target and attack myelin as a foreign body. This results in either total destruction or partial damage of myelin sheaths, this damages the Nodes of Ranvier causing a decrease in insulation of the axon which affects the speed of the conduction of action potentials as saltatory conduction is reduced (Goodkin et al., 1998). Remyelination can occur through repair by oligodendrocytes, which can potentially produce improvements in signs and symptoms. The new myelin sheath, however, may not be as thick as the original, decreasing electrical insulation resulting in less effective saltatory conduction (De Souza and Bates, 2004). Prolonged inflammation from repeated demyelination and incomplete remyelination can cause reactive astrocytosis and a decrease in new oligodendrocytes being formed (Guthrie and Nelson, 1995). The astrocytes produce a scar around the axon which is the typical sclerotic plaque of MS (Bjartmar et al., 2001).

Repeated relapses can also cause permanent changes in the brain via axonal loss, which can be multi-focal and a prominent determinant of progressive neurological disability (Bjartmar et al., 2003). Higher level of disability is associated with greater axonal loss but location of lesion is also a factor (Bjartmar et al., 2000). Damage to axonal tissue can start in the early stages of MS and can often be clinically silent (Ferguson et al., 1997, Kornek et al., 2000). This damage is caused either by a lack of trophic support from the myelin to the axon or from axonal transection (Coles et al., 1999). Axonal transection happens when the centre of an active inflammatory lesion transects an axon or axons, the subsequent distal axon then degenerates (Trapp et al., 1998), and, as there has been no demyelination of the distal axon, a hollow myelin sheath or ovoid remains (Evangelou et al., 2000). These redundant ovoids, which are visible on MRI, can then also degenerate (Bjartmar et al., 2001).

2.3.2 Secondary progressive Multiple Sclerosis

Secondary progressive MS is defined as a period of worsening disability of six or more months independent of relapses. There is currently no known physiological trigger for the onset of SPMS (Fitzner and Simons, 2010). It remains unclear if the development of SPMS is linked to the inflammatory phase of RRMS, if progression begins at onset or, if the development of SPMS and RRMS are independent of each other (Fitzner and Simons, 2010).

Whilst there are no known biomarkers, or clinical signs to discriminate between SPMS and RRMS, neurodegeneration is responsible for the irreversible deficits and progression of disability (Stadelmann et al., 2008, Trapp and Nave, 2008, Weiner, 2009). This neurodegeneration is independent of the inflammatory load experienced during the relapsing remitting phase, and accumulates when active lesions are less frequent (Fitzner and Simons, 2010). Hypointense lesion accumulation (black holes) indicate disease progression in SPMS (Truyen et al., 1996). Furthermore, an increase in the number and volume of lesions that are visible by MRI correlate with an increase in disability in the early stages of SPMS but not in later stages (Brex et al., 2002). This may be related to an overlapping

of the end of the relapsing remitting and the onset of the secondary progressive phase (Fitzner and Simons, 2010).

2.3.3 Primary progressive Multiple Sclerosis

Primary progressive MS is characterised by less inflammation than RRMS and SPMS (Smith and McDonald, 1999) as it is antibody driven, as opposed to lymphocyte driven. While hypointense lesions indicate disease progression in SPMS, they do not in PPMS (Truyen et al., 1996). There is an indication that axonal loss is more diffuse in PPMS, with white matter lesion load being lower in PPMS compared to SPMS. Remyelination occurs less frequently in PPMS compared to SPMS and RRMS (Lucchinetti et al., 1999) and demyelination without remyelination is a suggested mechanism for disease progression (Pender, 2004).

Clinically PPMS produces fewer MRI focal brain lesions compared to SPMS (Kidd et al., 1993, Thompson et al., 1990, Thompson et al., 1991), but the focal lesion load and rate in the spinal cord is equal between those with PPMS and SPMS (Kidd et al., 1996, Kidd et al., 1993). Therefore, generally a higher proportion of MRI lesion load in PPMS is in the spinal cord (Kidd et al., 1993), and axonal loss is also more diffuse compared to SPMS (Nijeholt et al., 1998, Thompson et al., 1990). This increased likelihood of axonal loss in the spinal cord is the probable cause of lower limb paraparesis being the most common onset symptom in PPMS (Thompson et al., 1997).

Despite fewer white matter lesions, PPMS often causes cerebral cortical atrophy (De Stefano et al., 2003). Cerebral cortical lesions are characterised by: demyelination, axonal transection, dendritic transection, neuronal apoptosis and cause less inflammation when compared to white matter lesions (Peterson et al., 2001). It is however unclear, the extent to which cerebral cortical damage contributes to disease progression in PPMS, but it could be linked to the proposed antibody mechanism instead of inflammation (Pender, 2004, Yim et al., 1994).

Spinal cord atrophy is found in all cases of MS (Kidd et al., 1993) but both brain and spinal cord atrophy are considered surrogate markers of progression in SPMS and PPMS as they strongly correlate with disability (Kalkers et al., 2001, Simon et al., 1999).

2.4 Diagnosis and history of diagnostic criteria

Diagnostic criteria for MS have changed over time, mainly due to advances in technology. There have been five sets of criteria with each newer set replacing the previous: the Schumacher criteria (Schumacker et al., 1965), the Poser criteria (Poser et al., 1983) and the McDonald criteria (McDonald et al., 2001). The latter were subsequently revised in 2005 (Polman et al., 2005), and again in 2010 (Polman et al., 2011).

The Schumacher criteria categorised diagnosis as clinically definite, probable and possible cases of MS. The criteria for a clinical definite diagnosis were all of the following: two or more areas of central nervous system involvement with clinical signs; white matter lesions; either two relapses of greater than 24 hours in length separated by a month or a steady progression of disability; aged between 10 and 50 years old and no other possible diagnosis (Schumacker et al., 1965).

The Poser criteria further defined an MS attack or relapse and introduced the criterion of laboratory evidence in the form of oligoclonal bands in cerebral spinal fluid. The Poser criteria had five categories of MS diagnosis: clinically definite, laboratory supported clinically definite, clinically probable, laboratory supported clinically probable and no MS (Poser et al., 1983).

The McDonald criteria introduced the criteria of dissemination in space and time as evidence by MRI and thus increased sensitivity of diagnosis. The McDonald criteria had three categories of MS diagnosis: definite, possible and not MS (McDonald et al., 2001). The McDonald criteria also created a new category for a CIS. A revision of the McDonald criteria further defined an MS attack (Polman et al., 2005), and the most recent revision from 2010 is considered to be the

current gold standard in diagnosis of MS (Polman et al., 2011). The 2010 revised McDonald criteria allow for diagnosis of MS in the absence of MRI evidence when there are two distinct MS attacks, and it further allows diagnosis with just one attack if there is definitive dissemination in both space and time upon MRI. However, it is not possible to diagnose MS in the absence of an attack (Table 2-1). Despite the changes in diagnostic criteria, the diagnosis of MS has always been dependent on exclusion of any other condition by differential diagnosis and a need for dissemination in time and space of lesions of white matter, signs and symptoms.

Table 2-1 Revised McDonald Criteria for the diagnosis of MS. Adapted from Polman et al (2011)

Clinical presentation	Additional data needed for MS Diagnosis
$\geq$ 2 attacks with clinical evidence of $\geq$ 2 lesions or objective clinical evidence of 1 lesion with historical evidence of a prior attack	None
$\geq$ 2 attacks with objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: MRI evidence of at least one inactive lesion in at least 2 of the following areas of CNS: periventricular, juxtacortical, infratentorial, spinal cord. Or await a further attack implicating a different CNS site
1 attack with objective clinical evidence of $\geq$ 2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic active and non-active lesions on MRI or a new inactive or active lesion on follow up MRI. Or await a second clinical attack.
1 attack with objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and dissemination in time as described above
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria: 1. MRI evidence of dissemination in space in the brain in at least one of the following areas: periventricular, juxtacortical, infratentorial. 2. MRI evidence of dissemination in space of at least two lesions in the spinal cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Abbreviations: MRI: magnetic resonance imaging; CNS: central nervous system; CSF: cerebral spinal fluid

2.5 Prognosis and onset of secondary progressive Multiple Sclerosis and progression of disease

An individual with RRMS will typically have mild to moderate disability (Bejaoui and Rolak, 2010, Scalfari et al., 2010). However, if a person with RRMS goes on to develop SPMS, or has PPMS their disability will steadily worsen over time (Lublin and Reingold, 1996).

The risk of developing SPMS from RRMS rises by 9% every five years and quadruples after 20 years (Eriksson et al., 2003). Other risk factors for developing SPMS are the age of onset (>30 years old), a higher level of disability, being male, high early relapse rate (more than two relapses in first two years) (Pokryszko-Dragan et al., 2008), and early signs of cerebellar or brainstem lesions (Scalfari et al., 2010). A high early relapse rate and brainstem lesions are also strong predictors of long term disability (Scalfari et al., 2010, Scalfari et al., 2014).

The average time for developing SPMS from RRMS is 15.2 years since diagnosis (Scalfari et al., 2013). The transition from RRMS to SPMS is not always clear as it can be difficult to distinguish between progression of symptoms and the symptoms of relapses. Some people may experience a complete cessation of relapses and a steady progression of disability whilst others may continue to experience relapses with some transient recovery along with the steady progression (Lublin and Reingold, 1996). A diagnosis of SPMS is made on signs and symptoms as opposed to imaging: this lack of official clinical markers in established SPMS means that there is no clear pathophysiological line between RRMS and SPMS and a mixed presentation often leads to a blurred transition between the two (Fitzner and Simons, 2010). As the transition from RRMS to SPMS often has an overlap with no clear distinction between the two forms of MS, this could potentially lead to people with SPMS still being classed as RRMS, or people with RRMS being classed as SPMS earlier than they should be. This potential misclassification of people with MS may lead to people being included in, or excluded from, research projects that have a specific type of MS as an inclusion criterion.

2.6 Measurement of disability in Multiple Sclerosis

Disability measurement in MS has developed over the years. The Extended Disability Status Scale (EDSS) is the most commonly used measurement but has come under criticism for being reliant on mobility in higher scores (Hobart et al., 2000). Other outcome measures have been developed including the Patient Determined Disease Steps (PDDS) and the Multiple Sclerosis Impact Scale (MSIS-29) the latter of which measures the impact of MS on the individual. Both of these are self-report measures, which increase the ease of application, and while the PDDS is also reliant on mobility, the MSIS-29 includes questions related to function and the psychological impact.

2.6.1 Extended Disability Status Scale

The EDSS is most commonly used measurement of disability in people with MS. It is a 20 point ordinal scale ranging from 0 – 10 with 0.5 increments. It categorises impairment in the following domains: pyramidal, cerebellar, brainstem, sensory, bladder and bowel, cerebral, visual and other (Kurtzke, 1983). Despite measuring disability in different domains, after a score of 4.0, rises in score are dependent on mobility. Scores of 0-4.5 are fully ambulatory, 5.0-8.0 are of worsening ambulation, 8.5–9.5 are restrained to bed or chair with worsening independence and 10.0 is death due to MS. The EDSS requires a clinician to be Neurostatus™ trained to carry out the assessment.

The EDSS is reliable with an inter-rater interclass correlation of 0.78 but the intra-rater interclass correlation has been found to vary between 0.62 and 0.94 (Hobart et al., 2000). Furthermore it is not sensitive to change and, as it is focused on mobility as scores increase, it may not reflect any improvements in function (Hobart et al., 2000). Due to this lack of sensitivity to change patients often cluster around bands of 3.0-4.0 and 5.0-6.0 (Sharrack et al., 1999). Despite these criticisms and limitations, the EDSS is still widely used in MS literature as a measure of disability both for screening and as an outcome measure.

2.6.2 Patient Determined Disease Steps

The PDDS is a self-administered measure that provides an ordinal score from 0-9, in 1 point increments, and is focussed entirely on mobility (Marrie and Goldman, 2007). It was developed from the Disease Steps (Hohol et al., 1995), by the North American Research Committee on Multiple Sclerosis Registry to use as part of their online data collection. The PDSS correlates moderately with EDSS (EDSS below 4.5 (rho = 0.641) and above 4.5 (rho = 0.688)) (Learmonth et al., 2013). The main advantage of the PDDS is that it does not require a physician to administer, unlike the original Disease Steps measure. However, like the EDSS it is heavily reliant on mobility and may not reflect function.

2.6.3 The Multiple Sclerosis Impact Scale - 29

The MSIS-29 is a 29 item self-report measure of disease impact. It is divided into two sections: the first 20 questions concern the physical impact of MS and the final 9 questions the psychological impact of MS. A higher score indicates a greater impact of disease. Each question is answered using a 5-point Likert scale and responses are given in relation to the previous two weeks (Hobart et al., 2001). The original version of the MSIS-29 was updated in 2009. Version 2 of the MSIS-29 is similar to version 1 but is answered using a 4-point Likert scale (scored 1-4), these are 'not at all', 'a little', 'moderately' and 'extremely'. This gives the physical and psychological impact sub-scales scores of 20-80 and 9-36 respectively (Hobart and Cano, 2009).

The physical sub-scale of the MSIS-29 version 1 was found to correlate moderately with EDSS (Spearman's rank coefficient 0.63) with correlation increasing with higher scores (higher physical impact) (Gray et al., 2009). The MSIS-29 version 1 is sensitive to change when compared to the EDSS with larger changes producing exponentially larger changes in MSIS-29 scores. For example a 0.5 change in EDSS approximately equates to 5 points in MSIS-29 but a change of

2 or more equates to a change of approximately 40 points in the MSIS-29 (McGuigan and Hutchinson, 2004).

In terms of the physical subscale of MSIS-29 version 1 the Minimal Clinical Important Difference (MCID) has been reported as a decrease of 7 points for those with an EDSS of 0.0 – 5.0 and a decrease in 8 for those with an EDSS of 5.5 - 8.0 (Costelloe et al., 2007a). In the psychological sub-scale of version 1, a decrease of 6 or more is deemed to be clinically significant (Widener and Allen, 2014). There is no available MCID for the sub-scales used in MSIS-29 version 2. The primary advantages of the MSIS-29 over the EDSS is that it does not require training to administer and can be administered in 10-15 minutes as opposed to a 30-45 minute assessment for the EDSS.

2.7 Clinical features, symptoms and treatment of Multiple Sclerosis

Clinical features and symptoms of MS include, but are not restricted to, mobility and motor problems, sensory disturbance, pain, spasticity and spasms, fatigue, visual disturbances, bladder and bowel problems, cognitive and emotional problems, sexual dysfunction and trouble swallowing (McDonald et al., 2001).

2.7.1 Mobility and motor problems

Mobility is defined as any bodily movement that creates a change in bodily position (World Health Organisation, 2009) and mobility problems are often the most visible sign of MS (Sutliff, 2010) with approximately 25% of the MS population being non-ambulatory (Einarsson et al., 2003). Initially mobility impairment usually presents as a reduction in gait speed and quality (Freeman, 2001). Motor problems can arise from muscle weakness, spasticity, tremors or ataxia due to cerebellar lesions and which impact on mobility (Koch et al., 2007). Ataxia can arise from decreased input into the cerebellum from afferent sensory input from spinal cord lesions as well as decreased output from demyelinated efferent cerebellum nerves (Schmahmann, 2004).

Difficulty in walking has been shown to reduce physical activity in people with MS (Motl et al., 2005), be directly correlated with disability levels (Kobelt et al., 2006), and is the largest prognostic factor in disability (Damasceno et al., 2013). The earlier an individual requires a walking aid the earlier they will be confined to a wheelchair (Tremlett et al., 2005). While the prevalence of mobility problems is similar between PPMS and SPMS, in PPMS lower limb weakness is more often one of the initial presenting symptoms (Thompson et al., 1997). This is due to the previously mentioned predominance of spinal cord lesions in PPMS compared to SPMS (section 2.3.3).

2.7.2 Sensory disturbance

Sensory symptoms are often one of the initial symptoms of MS (Murray, 2006) especially in cases of PPMS (Thompson et al., 1997). These can present as decreased sensation or complete numbness or paraesthesia ("pins and needles", tingling or burning) (Gaby, 2013). Sensory symptoms may arise from damage to both afferent and efferent pathways which can cause secondary issues with sensory feedback and proprioception; leading to sensory based ataxia (Schmahmann, 2004).

2.7.3 Pain

Evidence suggests that MS pain affects up to 86% of all people with MS (O'Connor et al., 2008) and may be the most pharmacologically treated symptom accounting for up to 30% of all drug use (Brichetto et al., 2003). Approximately 69% of people with MS are affected by chronic pain (Kalia and O'Connor, 2005, Khan and Pallant, 2007), but despite the high prevalence of MS-related pain it is rarely the initial symptom at onset (Hadjimichael et al., 2007, O'Connor et al., 2008).

MS pain is usually considered within four categories: continuous central neurogenic pain, intermittent neurogenic pain (including trigeminal neuralgia, Lhermitte's sign, and glossopharyngeal neuralgia), musculoskeletal pain (pain

arising from tonic spasms or spasticity, or contractures) and a mixture of both non-neurogenic and neurogenic pain (O'Connor et al., 2008).

Central pain is the most common type of pain experienced (Osterberg et al., 2005) and a commonly held opinion is that all primary MS pain syndromes arise from the central nervous system and that neurogenic pain, from the peripheral nervous system, is less frequent (O'Connor et al., 2008).

Pain phenomena unique to MS include the MS 'hug' or 'girdle', Lhermitte's sign, and trigeminal neuralgia. The MS 'hug' is a tightness and compression feeling in the chest (O'Connor et al., 2008). Lhermitte's sign is the spontaneous discharge of mechanically sensitive axons causing electric shock like sensations in the upper limbs or flashing lights (Brola et al., 2014). Trigeminal neuralgia is characterised by severe pain in the face or head arising from the trigeminal nerve, which can last from seconds to hours, while optic neuritis will often present as pain with eye movement as one of its symptoms (Foley et al., 2013).

A definite physiological mechanism of central pain has not been found (Brola et al., 2014) but demyelination and diffuse axonal damage can lead to central hyper-excitability of central nociceptor pathways (Solaro et al., 2013, Truini et al., 2012). Pain is a complex symptom, as many other symptoms in MS, and can be multifactorial in nature which requires an holistic treatment approach (Solaro et al., 2013).

2.7.4 Spasticity and Spasms

A European working group for spasticity defined spasticity as a "disordered sensorimotor control resulting from an upper motor neuron lesson, presenting as intermittent or sustained involuntary activation of muscles." (Pandyan et al., 2005). Spasticity is highly prevalent in people with MS (Barnes et al., 2003, Berger, 2013, Collongues and Vermersch, 2013, Oreja-Guevara et al., 2013, Rizzo et al., 2004) with some literature reporting prevalence rates as high as 80% (Rizzo et al., 2004) although a recent worldwide estimate stated prevalence at

around 40% of all people with MS (Collongues and Vermersch, 2013) with 40% of spasticity being moderate and 25% severe (Collongues and Vermersch 2013).

Although the pathophysiology of spasticity in MS is complex and not fully understood, (Amatya et al., 2013, Kheder and Nair, 2012, Pappalardo et al., 2006) the definition of intermittent or sustained activation of muscles is related to the hyper-excitability of afferent and efferent neural pathways which affect the activation of the muscle (Meca-Lallana et al., 2015). Diffuse axonal loss is correlated with an increase in excitability of the tendon stretch reflex and the severity of spasticity (Barnes et al., 2003). Worsening of spasticity is associated with disease and disability progression (Shakespeare et al., 2003).

Progression in disability due to spasticity, can impact negatively on quality of life and function through impact on mobility and function (Arroyo et al., 2013, Fernandez et al., 2011, Hemmett et al., 2004, Zettl et al., 2014). This decrease in independence is cited as one of the most worrying symptoms of people with progressive MS (Strupp et al., 2012). Despite the negative impact on mobility spasticity can, on occasion, provide physical support in cases of lower limb weakness and actually reduce disability in mild cases (Pappalardo et al., 2006). However, these cases are in the minority and in general, spasticity impacts negatively on quality of life and disability.

2.7.5 Fatigue

Fatigue is defined as abnormal tiredness or absence of energy, disproportionate to the task or normal effort required and impacts on routine or intellectual functions (Weinshenker et al., 1992). It is deemed clinically significant when it impairs activities of daily life or quality of life (Bakshi, 2003). Fatigue can, in MS, be the only symptom of a relapse (Flachenecker and Meissner, 2008) and is one of the most common symptoms affecting up to 75-95% of all people with MS with 50-60% citing fatigue as their most disabling symptom (Bakshi, 2003, Kos et al., 2008). However, fatigue is usually only cited as the most disabling symptom during low to moderate disability. When a person enters a progressive phase and becomes more disabled, mobility then becomes their most disabling symptom

(Strupp et al., 2012). Fatigue in MS can be classified as primary or secondary. Primary fatigue is a result of MS and secondary fatigue is usually a side effect of medications or physical deconditioning (Bakshi, 2003).

Fatigue can impact negatively on cognitive ability and quality of life (Krupp and Elkins, 2000). It can lead to a transition from full to part-time employment and increase the risk of unemployment (Simmons et al., 2010). MS-related fatigue has been linked to low mood and disability (Bakshi, 2003). It can be difficult to distinguish between primary and secondary fatigue as fatigue may be caused by other concomitant conditions such as depression (Bakshi et al., 2000), which may independently impact on quality of life (Janardhan and Bakshi, 2002), or as a side effect from disease modifying pharmacological treatments (Mohr et al., 2003). Fatigue is inversely correlated with cardiovascular fitness and related to deconditioning (Valet et al., 2016). In MS, when fatigue is caused by deconditioning, it is regarded as secondary fatigue (Khan et al., 2014, Kos et al., 2008, MacAllister and Krupp, 2005).

Current evidence of non-pharmacological treatments in treating fatigue in MS is limited mainly by methodological weaknesses (Amato and Portaccio, 2012). The pathophysiology of MS-related fatigue is not fully understood but is likely multifactorial with links to both the central and peripheral nervous systems, immunological and neuroendocrine factors (Amato and Portaccio, 2012, Gottschalk et al., 2005, Roelcke et al., 1997). There have been links made between fatigue and lesions in the central nervous systems including diffuse axonal damage (Tartaglia et al., 2004), lesions in the basal ganglia and the hypothalamus (Comi et al., 2001, Filippi et al., 2002, Roelcke et al., 1997), and cortical atrophy (Pellicano et al., 2010).

The multifactorial nature of fatigue in MS, and the lack of definitive physiological mechanisms create many different possible routes of intervention: pharmacological, behavioural therapy and exercise interventions. However, MS related fatigue is difficult to treat and the source of the fatigue and physiological impact of the intervention may limit efficacy of interventions (Amato and Portaccio, 2012). Nonetheless, exercise has been recommended as part of a multi-factorial approach in the management of secondary fatigue that has been caused by deconditioning (Asano and Finlayson, 2014), with evidence

suggesting that aerobic exercise can improve general fatigue symptoms (Latimer-Cheung et al., 2013). This improvement comes from the impact that exercise, and fitness, can have on function, and quality of life by decreasing the physical burden of tasks (Andreasen et al., 2011).

2.7.6 Visual disturbances

Optic neuritis, inflammation of the optic nerve, affects approximately 40% of people with MS at some point in their lifetime (Roodhooft, 2009). Symptoms can include diplopia, blurred or "smeary" vision, spotted vision or posterior eye pain (Optic Neuritis Study, 2008). Optic neuritis is often the very first presentation of MS and is used in early diagnosis of the disease (Halilovic et al., 2014).

2.7.7 Bladder and bowel problems

Bladder problems affect approximately 75% of people with MS with symptoms including increased urgency, increased frequency, hesitancy, retention and incontinence (Browne et al., 2015). Incontinence may be perpetuated, and in some cases created, by mobility issues if a person is in a progressive phase of MS with worsening disability (Andrews and Husmann, 1997). The most common bowel problem is constipation, which has two main causes: directly due to decreased peristalsis of the bowel due to demyelination or as a secondary issue from medication or an intentional decrease in fluid intake to limit urinary incontinence (Preziosi et al., 2014).

2.7.8 Cognition and emotional impairment

Cognitive impairment is a phenomenon only recognised in people in MS in the past 30 years (Amato et al., 2006). Cognitive symptoms can present in all subtypes of MS at any stage (Haase et al., 2003) and remission is rare (Amato et al., 2006). Cognitive impairments can have a large detrimental effect on an individual's quality of life by impacting on activities of daily life, independence

(for example driving), and making and maintaining social relationships (Amato et al., 2001b).

Whereas dementia and language deficits are rare, common cognitive issues include deficits in learning, memory, attention and processing speed, visuospatial abilities, and executive function (Bobholz and Rao, 2003, Chiaravalloti and DeLuca, 2008, Rogers and Panegyres, 2007). It is estimated that between 50% and 65% of all people with MS have some sort of cognitive impairment (Amato et al., 2006). People with PPMS, in particular, are affected by issues with memory, attention and processing and executive function (Camp et al., 2005). Cognitive impairment is associated with worsening physical disability (Lynch et al., 2005), time since diagnosis (Amato et al., 2001b), and progressive forms of MS (Achiron et al., 2005) and it has been proposed that cognitive impairment symptoms are signs of disease activity in the brain (Patti, 2009).

In people with SPMS there is a weak relationship between cognitive problems and both white matter lesions and brain atrophy (Benedict et al., 2006, Benedict et al., 2004). In people with PPMS memory problems and attention deficits correlate with diffuse brain T1 and T2 lesion load but not with whole brain atrophy (Ukkonen et al., 2009). In addition, in those with PPMS brain atrophy and diffuse white matter damage correlate with deficits in complex reasoning, which is part of executive function, (Camp et al., 2005, Camp et al., 1999, Ukkonen et al., 2009) and grey matter lesion load correlates with general cognitive dysfunction (Tur et al., 2011).

A study of all subtypes of people with MS, but predominantly RRMS, found that all participants displayed signs of cognitive reserve as measured by vocabulary (Sumowski et al., 2009) . In a follow up study, people with SPMS who had had what the authors described as ‘life intellectual enrichment’ showed cognitive reserve (Sumowski et al., 2012). This attenuated the negative effects of MS on their cognitive efficiency compared to similar patients with less cognitive reserve and improved their memory more than similarly matched healthy subjects with less cognitive reserve.

Depression in MS, like fatigue, can impact negatively on quality of life and can be separated into secondary and primary depression (Amato et al., 2001a). Primary depression is caused as a direct result of an MS lesion whilst secondary depression is caused as a result of an MS symptom, a situation, or as a side effect of medication (Holden and Isaac, 2011). People with MS may also experience emotional lability, or the pseudobulbar effect, and display amplified, non-appropriate or incongruent emotional responses (Cummings et al., 2006).

2.7.9 Sexual dysfunction

Sexual dysfunction is higher in people with MS compared to the general population (Schmidt et al., 2005), and is a recognised problem in people with MS (Fletcher et al., 2009). It may arise directly from impotence or decreased sensation and sensitivity or as a secondary symptom from other issues such as pain, spasticity, tremor, incontinence, weakness or depression (Previnaire et al., 2014). The most common primary symptom of sexual dysfunction is impotence in men (Guo et al., 2012) and delayed orgasm in women (Merghati-Khoei et al., 2013). Sexual dysfunction also has the potential to cause secondary issues with mood and depression (Fletcher et al., 2009).

2.7.10 Dysphagia

Dysphagia is a disorder of the swallowing reflex and can result in aspiration of food or liquid into the lungs (Brady, 2008). Prevalence of dysphagia amongst people with MS rises significantly with disability level and the onset of progressive MS, with approximately 5% of those with an EDSS of 2-3 and 65% of those with an EDSS of 8.0-9.0 experiencing the symptom (De Pauw et al., 2002).

2.8 Pharmacological treatments for multiple sclerosis

There are three main categories of pharmacological treatments available for MS: disease modifying drugs, corticosteroids and drugs for symptomatic control.

Until recently, disease modifying drugs were only effective in those with RRMS and not in those with a progressive form of the disease. In March 2017 however, Ocrelizumab, which has been shown to reduce progression of disease in people with PPMS by up to 25% (Montalban et al., 2015), was approved by the Food & Drug Administration in the United States of America for use in people with RRMS and PPMS (U.S. Food & Drug Administration, 2017) and in November 2017 was approved by the European Medicines Agency for use in early PPMS (European Medicines Agency, 2017). It is however, not yet available on the National Health Service in the UK. The purpose of disease modifying drugs is to decrease inflammation via immunosuppression, which in turn decreases the autoimmune attack on myelin, the relapse rate and the severity of any relapse experienced. A decreased relapse rate can extend the latency period of subsequent development of SPMS, thus slowing disease progression (Martinelli Boneschi et al., 2013), but not necessarily long-term disability (Brownlee and Miller, 2014). Use of disease modifying drugs in cases of CIS may delay development of MS but may, in some cases, result in patients being treated for MS when the disease is not present (Brownlee and Miller, 2014). A list of common disease modifying therapies and their brand names can be seen in Table 2-2.

Table 2-2 List of disease modifying therapies, their common brand names, sub-types of MS for which they are suitable and their availability in the UK

Name of DMTs	Brand names	MS sub type	Available in UK
Beta-interferon	Rebif, Avonex, Betaferon	RRMS	Yes
Glatiramer acetate	Copaxone	RRMS	Yes
Dimethyl fumarate	Tecfidera	RRMS	Yes
Teriflunomide	Aubagio	RRMS	Yes
Natalizumab	Tysabri, Antigren	RRMS	Yes
Fingolimod	Gilenya, Novartis	RRMS	Yes
Mitoxantrone	Novantrone	RRMS	Yes
Alemtuzumab	Lemtrada	RRMS	Yes
Olecrilizumab	Ocrevus	RRMS, PPMS	No

Abbreviations: RRMS: relapsing remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis

Side effects of disease modifying drugs vary depending on the individual. Some non-serious possible side effects include depression, fatigue, malaise and flu-like symptoms shortly after initially beginning treatment. However, over time the severity of the side effects can often wane and become more manageable (Scolding et al., 2015). On occasion however these side effects can out-weigh the benefits. Additionally some disease modifying drugs such as Fingolimod, Teriflunomide and Alemtuzumab have more serious potential side effects such as bradycardia, blood clotting, changes in liver function and an increased risk of leukaemia and progressive multifocal leukoencephalopathy (Cohen et al., 2010, Cohen et al., 2012, Vermersch et al., 2014, Baldwin and Hogg, 2013, Goodin et al., 2003).

Corticosteroids can increase the speed of recovery from a relapse but will not affect the magnitude of recovery, decrease residual deficit, slow down the progression of the disease or affect long term disability level (Brusaferri and Candelise, 2000). The pathological mechanism of aiding recovery is not fully known but it is theorised that corticosteroids either suppress the immune system

or decrease inflammation around the damaged nerve tissue (Myhr and Mellgren, 2009).

While there is now a pharmacological treatment for people with PPMS which is available in the United States of America, this is not yet available in the UK. Furthermore there are no pharmacological treatments, to slow disease progression, for people with SPMS (Fox et al., 2012). Thus pharmacological treatment in cases of progressive MS usually focuses around symptom management (Scolding et al., 2015).

Pharmacological treatments for symptoms include Fampridine, which can improve mobility. A recent review found short term improvements in the timed 25 foot walk test and improvements in the 12 item MS Walking Scale (Kim, 2017). Several drugs are available for treating fatigue: these include Amantadine and Modafinil. Amantadine has been shown to be effective in small doses (NICE, 2014b). Modafinil is often prescribed off-label for the treatment of MS fatigue. Research has however, shown inconsistent results and a meta-analysis called for larger and methodologically stronger trials to confirm or deny its efficacy in treating MS fatigue (Sheng et al., 2013). Neuropathic MS pain can be treated with anticonvulsants such as Gabapentin and tricyclic antidepressants such as Amitriptyline and analgesic painkillers can be used for musculoskeletal pain (NICE, 2017). Muscle relaxants such as Baclofen or Diazepam and anticonvulsants such as Gabapentin are used in the treatment of spasticity (NICE, 2014b).

2.9 Employment in Multiple Sclerosis

Unemployment is common in people with MS which can have a detrimental effect on quality of life (Boe Lunde et al., 2014). In addition there is a strong inverse correlation with physical disability and working ability (Krause et al., 2013, Moore et al., 2013). Generally those with MS have a lower level of employment compared to the general population: 41.9% compared to 76.9% (Ford et al., 2012). However, there are similar percentages of people with MS registered as permanently sick as the general population: 29.8% compared to

24.5% (Ford et al., 2012). It is common however, for people with MS to move initially from full-time employment to part-time employment (Jennum et al., 2013). Busche et al. (2003) reported that 66% of their sample who were employed had RRMS, and 78% of those who were unemployed had a progressive form of MS. They found that predictors of becoming unemployed included a rise in disability; having a progressive form of MS with SPMS having a higher risk than PPMS; being older and with longer disease duration. Overall the people most likely to be made unemployed because of their MS were those who were older than 39 years old, had moderate disability or SPMS (Busche et al., 2003).

Both Busche et al. (2003) and Ford et al. (2012) agreed that as disability, particularly physical disability, increased the less likely the person with MS was of being employed. This likelihood is perpetuated if an individual has progressive MS, and in particular SPMS.

2.10 Economic impact of Multiple Sclerosis

Multiple Sclerosis can be an economic burden to the individual and their families, the health service and society. This burden includes direct medical costs such as visits to outpatient clinics, hospital admissions, assistive devices, pharmaceutical prescriptions and long-term care (Naci et al., 2010). Furthermore indirect medical costs can be incurred including modifications to home or car, transport, and informal care. There is also a cost to the economy in lower employment, moving from full time to part time, loss of earnings, decreased tax receipt to the economy and through receipt of disability benefits (Jennum et al., 2013). A rise in disability level also carries an economic cost both in care and in loss to the economy, which doubles as EDSS moves from 2.0 to 4.0 and triples from 4.0 to 6.5 (Trisolini et al., 2010).

A review of the literature of medical costs of MS in the US from 1999-2008 found that cost per MS patient per year ranged from $8,528-54,244. Of these costs approximately 77% were direct medical costs and 23% were indirect medical costs. This direct costing placed MS second only to congestive heart failure in being the most costly chronic condition in the United States of America

(Adelman et al., 2013). Another study in the US found that cost of a relapse increased with severity of relapse and a higher relapse rate was associated with higher costs both directly and indirectly (Parise et al., 2013).

The cost of MS is rising over time; mainly attributed to the rise in cost of disease modifying therapies. An expert editorial reported that the cost of disease modifying drugs in the US have, over the past 20 years, risen at rates that are five to seven times greater than that of prescription drug inflation (Hartung et al., 2015). They also noted that newer disease modifying drugs entered the market at 25-60% more expensive than 'first generation' disease modifying drugs. This however, would not impact on the cost of progressive MS who should not be taking disease modifying drugs (Scolding et al., 2015).

There is very little information regarding the cost of progressive forms of MS but a report published by the Multiple Sclerosis International Federation (MSIF) on the global impact of MS noted that caregivers of people with progressive MS had four times the absence from work of their counterparts who cared for those with RRMS (Trisolini et al., 2010).

2.11 Multiple Sclerosis and mortality

It was previously thought that people with MS had a life expectancy comparable to that of the general population, however a review of cohort studies found life expectancy to be five to ten years shorter if an individual has MS (Ragonese et al., 2008). Furthermore a Danish study found that over half of those with MS died as a result of their MS (Bronnum-Hansen et al., 2004).

The literature of survival times from diagnosis is conflicting. A review in 2008 found that survival times from diagnosis was the same regardless of age at diagnosis (Ragonese et al., 2008) but a more recent study found that a younger age at diagnosis correlated with a longer survival time but overall a younger mortality age (Rodriguez-Antiguedad Zarranz et al., 2014). The converse was also true that an individual diagnosed later on in life would have a shorter survival time from diagnosis but overall die at an older age.

2.12 Multidisciplinary care

Multidisciplinary care has been shown to be effective in neurological conditions such as stroke (Greener and Langhorne, 2002, Langhorne et al., 2002) and traumatic brain injury (Turner-Stokes et al., 2005). A Cochrane review concluded that the holistic approach of multidisciplinary care in MS did not affect impairment but it did produce a positive increase in activity and participation and thus improved quality of life. The authors also noted that this had a positive effect on the general health and social engagement of carers of people with MS (Khan et al., 2007). Multidisciplinary care has also been recommended specifically for both SPMS (Giovannoni, 2004) and PPMS (Khan et al., 2011). Both position papers addressed the management of these progressive subtypes and recommended that management and interventions focussed on symptoms, addressed mental health aspects, and quality of life.

Multidisciplinary care can vary in its setting, interventions and intensity. What is common is the holistic and cross-disciplinary approach with the involvement of the patient and patient centred goals. This is vital in MS, due to the variation in clinical presentation and needs of the patient. Since there is no available effective treatment for slowing the progression of progressive MS (Compston and Coles, 2008), treatment often focuses on symptom management. Such treatment can be pharmacological or non-pharmacological. Non-pharmacological symptom management often takes the form of rehabilitation (Dix and Green, 2013). Access to MS specialist services including physiotherapy is part of the current National Institute for Health and Care Excellence (NICE) guidelines (NICE, 2014b) and the Health Care Improvement clinical standards for neurological conditions in Scotland (Healthcare Improvement Scotland, 2009). These guidelines and standards state a person with MS should receive a regular review of their MS at least once a year. Under the NICE guidelines, published in 2014, this review can be undertaken by any health professional including general practitioners, and not necessarily a specialist in MS. However, the level of access to a regular review by people with progressive MS was unknown before the research described by this thesis was conducted.

2.13 Physiotherapy for Multiple Sclerosis

According to the Chartered Society of Physiotherapy, "Physiotherapy helps restore movement and function when someone is affected by injury, illness or disability." and that "Physiotherapists help people affected by injury, illness or disability through movement and exercise, manual therapy, education and advice." (Chartered Society of Physiotherapy, 2013). There is evidence indicating positive benefits of using physiotherapy in the rehabilitation of people with RRMS. Several review papers concluded exercise therapy to be generally beneficial for people with MS who are not suffering a relapse, (Dalgas et al., 2008, Latimer-Cheung et al., 2013, Rietberg et al., 2005), as well as having positive effects on fatigue (Andreasen et al., 2011, Pilutti et al., 2013), health related quality of life (Motl and Gosney, 2008) and muscle strength (Kjolhede et al., 2012), in those with a mild to moderate disability. Further reviews have found physiotherapy to have a positive effect on balance and mobility (Hogan and Coote, 2009, Paltamaa et al., 2012, Toomey and Coote, 2012). Although the evidence for physiotherapy for people with MS is strong for those with mild to moderate disability it is less compelling for people with moderate to severe disability due to methodological weaknesses in the studies (Hogan and Coote, 2009, Toomey and Coote, 2012).

Whilst some of these reviews considered their results in terms of disability levels, none have made a distinction between RRMS and progressive MS. This is a large gap in the literature, in relation to the efficacy of physiotherapy, especially as the physiology of RRMS and progressive MS and between SPMS and PPMS, is notably different. At the time of this thesis, there were no published reviews examining the evidence for physiotherapy for the rehabilitation of people with progressive MS. Furthermore, rehabilitation of people with progressive MS has been identified as one of the research priorities of the International Progressive MS Alliance (section 2.14), who have called for more intervention trials in this patient group and specifically for those with a higher level of disability (Fox et al., 2012).

To summarise, the main gaps in the literature when the work within this thesis started were:

- There was no review of evidence of physiotherapy for the rehabilitation in people progressive MS
- Limited knowledge of access and use of clinical services, access to physiotherapists and regular reviews by people with progressive MS
- In people with progressive MS with a higher disability, there was a lack of rehabilitation intervention trials.

2.14 Research priorities in progressive Multiple Sclerosis

In 2012 two groups, the International Progressive MS Alliance and the MS Society with the James Lind Alliance, set out to broaden and deepen the research of MS in general and specifically progressive MS.

The International Progressive MS Alliance was established in 2012 as a collaboration between the Multiple Sclerosis International Federation and the MS Societies of five western countries with high incidences of MS: Canada, Italy, the Netherlands, the UK, and the United States of America. Its goals are:

1. To raise the profile and accelerate progress of research in progressive MS
2. Secure resources and globalise research funding
3. Inspire, galvanize and engage awareness in progressive MS research
4. Deliver operational excellence

In 2012 the International Progressive MS Alliance then set out its five key research priorities which can also be seen in Table 2-3.

The James Lind Alliance conducted a Priority Setting Partnership in the UK involving representatives of patients, carers, health professionals, and researchers (MS Society, 2014). The purpose of the Partnership was to establish the 10 most pertinent research questions regarding MS. A steering group oversaw

and conducted a survey completed by 507 individuals culminating in 1084 research questions. A year after collation the top 30 questions were discussed, face to face with key stakeholders, and then a steering group identified the 10 most important research questions (Table 2-3).

There is an overlap between the 10 most important research questions identified by the James Lind Alliance and the research priorities of the International Progressive MS Alliance. Of relevance to the research reported in this thesis, there is notably overlap between the research priorities of proof of concept clinical trial strategies, symptom management, and rehabilitation and the questions relating to mobility, cognition, physiotherapy, and fatigue. Other areas of overlap include the research priority of repurposing opportunities, identification and validation of targets and the questions of treatments to slow disability, the use of Vitamin D, the treatment of pain fatigue, cognition and mobility.

Table 2-3 10 most pertinent research questions from the James Lind Alliance and the top 5 key research priorities from the International Progressive MS Alliance

James Lind Alliance's top 10 research questions	International Progressive MS Alliance's key research priorities
1. Which treatments are effective to slow, stop or reverse the accumulation of disability associated with MS? 2. How can MS be prevented? 3. Which treatments are effective for fatigue in people with MS? 4. How can people with MS be best supported to self-manage their condition? 5. Does early treatment with aggressive disease modifying drugs improve the prognosis for people with MS? 6. Is Vitamin D supplementation an effective disease modifying treatment for MS? 7. Which treatments are effective to improve mobility for people with MS? 8. Which treatments are effective to improve cognition in people with MS? 9. Which treatments are effective for pain in people with MS? 10. Is physiotherapy effective in reducing disability in people with MS?	1. Identification and validation of targets and repurposing opportunities 2. Experimental models 3. Proof-of-concept clinical trial strategies 4. Clinical outcome measures 5. Symptom management and rehabilitation

2.15 Aims and objectives of the thesis

The overall aim of this thesis was to investigate the use of physiotherapy in the rehabilitation of people with progressive MS.

The objectives were:

Objective 1: to systematically review the available evidence to assess the efficacy of physiotherapy in the rehabilitation of people with progressive MS.

Objective 2: to investigate the views of people with progressive MS with regards to physiotherapy; more specifically access, use, perceived efficacy and preferred delivery of physiotherapy; and access and use of other MS specialists and clinical services.

Objective 3: to conduct a feasibility trial of High Intensity Interval Training in people with progressive MS, to assess the effect that this has on both clinical and physiological outcomes, and compare this to traditional continuous moderate intensity training.

To achieve these objectives three studies were undertaken

Study 1: a systematic review of the available literature pertaining to physiotherapy and progressive MS.

Study 2: a nationwide online survey of people with progressive MS exploring access, delivery and opinion of physiotherapy and access to other MS clinical services and the use of Complementary and Alternative Therapies.

Study 3: a randomised controlled trial comparing high intensity interval training against continuous moderate intensity training in people with progressive MS.

The rationale and research questions for each study are discussed in chapters 3, 4, and 7.

Chapter 3 Physiotherapy rehabilitation for people with progressive Multiple Sclerosis: a systematic review.

As was stated at the end of the last chapter there had not been a systematic review of the literature examining the evidence for using physiotherapy in the rehabilitation of people with progressive Multiple Sclerosis (MS). This chapter will present the need for such a systematic review. The methods, results and discussion of the results will then be presented. This review has been published (Campbell et al. 2015. Physiotherapy rehabilitation for people with progressive Multiple Sclerosis: a systematic review. Archives of Physical Medicine and Rehabilitation, 97, 141-151.e3. (Appendix 1)) and presented in Sections 3.1 to 3.6. Since publication, there have been a number of new articles published assessing physiotherapy for people with progressive MS. The final section of this chapter will present the results from an updated search of the literature and discuss the impact of these newer articles on the conclusions drawn from the original systematic review.

3.1 Abstract

Objective: To assess the efficacy of physiotherapy interventions, including exercise therapy, for the rehabilitation of people with progressive Multiple Sclerosis.

Data Sources: Five databases (Cochrane Library, Physiotherapy Evidence Database (PEDro), Web of Science Core Collections, Medline, EMBASE) and reference lists of relevant articles were searched.

Study Selection: Randomised experimental trials which included participants with progressive multiple sclerosis and investigated a physiotherapy intervention or an intervention containing a physiotherapy element were included.

Data Extraction: Data were independently extracted using a standardised form and methodological quality was assessed using the PEDro scale.

Data Synthesis: Thirteen studies (described by 15 articles) were identified; scoring between 5 and 9 out of 10 on the PEDro scale. Eight interventions were assessed: exercise therapy, multi-disciplinary rehabilitation, functional electrical stimulation, botulinum toxin type A injections and manual stretches, inspiratory muscle training, therapeutic standing, acupuncture and body weight supported treadmill training. All studies, apart from one, produced positive results in at least one outcome measure, however, only one article used a power calculation to determine their sample size and due to 'drop outs' the results were subsequently underpowered.

Conclusions: This review suggests that physiotherapy may be effective for the rehabilitation of people with progressive Multiple Sclerosis. However, further appropriately powered studies are required.

Keywords: Multiple Sclerosis, physical therapy modalities, exercise, rehabilitation, review

3.2 Introduction

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease of the central nervous system resulting in grey matter and axonal loss (Compston and Coles, 2008, Noseworthy et al., 2000). Currently, there are an estimated 130,000 cases of MS in the UK with an incidence of 11.52 per 100,000 women and 4.84 per 100,000 men (Mackenzie et al., 2014). Approximately 15% of all individuals with MS are diagnosed with Primary Progressive MS (PPMS) and 80% of those diagnosed with Relapsing Remitting MS (RRMS) go on to develop Secondary Progressive MS (SPMS) (Compston and Coles, 2002). There is a strong evidence base for interventions for the treatment of people with RRMS but whilst studies are currently ongoing there are limited effective treatments for people with progressive MS (Fox et al., 2012). The Progressive MS Alliance have highlighted this area as a priority, especially for those with a higher level of disability (Fox et al., 2012).

There is a growing body of literature investigating the benefits of physiotherapy (a physical intervention that may be used by a physiotherapist, including physical activity and exercise interventions) in the rehabilitation of people with MS. In a series of review papers, exercise therapy and physical activity have been shown to be generally beneficial to those with MS who are not suffering a relapse (Dalgas et al., 2008, Latimer-Cheung et al., 2013, Rietberg et al., 2005), as well as having positive effects on fatigue (Andreasen et al., 2011, Pilutti et al., 2013), health related quality of life (Motl and Gosney, 2008) and muscle strength (Kjolhede et al., 2012) in those with a mild to moderate disability. Physiotherapy has also been shown to have a positive effect on balance and mobility (Hogan and Coote, 2009, Paltamaa et al., 2012, Toomey and Coote, 2012). However, when the level of disability increases efficacy of physiotherapy is less compelling (Hogan and Coote, 2009, Toomey and Coote, 2012). Whilst some studies have considered their results in terms of disability levels, none have made a distinction between RRMS and progressive MS. To date, there has not been a published review examining the evidence for physiotherapy for the rehabilitation of people with progressive MS. Consequently, the aim of this systematic review is to assess the efficacy of physiotherapy rehabilitation for people with progressive MS.

3.3 Methods

In December 2014 a search was conducted of the following electronic databases: the Cochrane Library, Physiotherapy Evidence Database (PEDro), Web of Science Core Collections, Medline and Embase. No restrictions were placed on publication date and studies were limited to English language only. Individual search strategies were made up of keywords and Medical Subject Headings (MeSH) headings (Table 3-1). Reference lists of relevant articles were also searched.

To be included in the review, articles had to: be published in English, include solely participants with progressive forms of MS or where there was a combination of types of MS distinct results for the different types of MS were presented, evaluate a physiotherapy intervention(s) or an intervention

containing a physiotherapy element, have randomised participants, have a comparison group and use at least one objective outcome measure. Articles were excluded if they were non-human studies, conference abstracts or posters. Articles were initially screened by title and abstract. Full articles were then read. When there was ambiguity in meeting the inclusion criteria the authors were contacted for clarification.

Quality assessment (external validity, internal validity and the reporting of statistics) was assessed using the PEDro scale which has been shown to be reliable and valid in rating methodological quality of studies (de Morton, 2009, Maher et al., 2003). The 11 point scale was given a score out of ten (no point was awarded for the initial item of stating inclusion and exclusion criteria) as per the guidelines. Scoring was carried out by three reviewers (EC, LP and EHC). A pilot quality assessment was conducted to ensure consistency where all three reviewers read and independently scored one paper, following which, scoring was discussed and agreed. Each article was then scored independently by two reviewers and scores compared. When there was a discrepancy in score, differences were agreed via discussion which included the third reviewer. Quality assessment was entirely based on the content of the study in the published article. When two articles were from the same study but reported different outcome measures they were combined and considered as a single study. Data extraction was done independently using a standardised form into evidence tables. The following data were extracted: study design, sample size, drop-out rate, type of MS of participants, Expanded Disability Status Scale (EDSS) range (Kurtzke, 1983), intervention type, length, frequency, setting, time points of measurement, control intervention, outcome measures, baseline measurements and main findings.

Table 3-1 Search strategies for electronic databases

Database	Search Strategy
Cochrane library	(Progressive near/2 ("multiple sclerosis" or MS)) AND ((MeSH descriptor: [Physical Therapy Modalities] explode all trees) OR(MeSH descriptor: [Rehabilitation] explode all trees) OR (MeSH descriptor: [Exercise] explode all trees) OR (MeSH descriptor: [Resistance Training] explode all trees) OR (MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees) OR (MeSH descriptor: [Electric Stimulation] explode all trees) OR(MeSH descriptor: [Acupuncture] explode all trees))
Web of Science Core Collections	((progressive NEAR/2 (MS OR "Multiple Sclerosis")) AND ((physiotherap* OR "physical therapy") OR (rehabilit*) OR (exercise OR training) OR ("electrical stimulation" OR FES OR NMES OR TENS OR "neuromuscular stimulation") OR (acupuncture)
Embase via Ovid	((progressive adj2 ("multiple sclerosis" or MS)).mp.) AND ((home physiotherapy OR physiotherapy) OR (prevention OR rehabilitation OR therapy OR rehabilit*.mp. OR rehabilitation center OR rehabilitation care OR breathing exercise OR muscle exercise OR arm exercise OR treadmill exercise OR aerobic exercise OR static exercise OR leg exercise OR isokinetic exercise OR closed kinetic chain exercise OR open kinetic chain exercise OR exercise.mp. OR exercise tolerance OR isometric exercise OR isotonic exercise OR aquatic exercise OR dynamic exercise OR stretching exercise OR anaerobic exercise OR exercise OR nerve stimulation OR electrostimulation therapy OR electroacupuncture OR functional electrical stimulation OR neuromuscular electrical stimulation OR transcutaneous nerve stimulation OR acupuncture OR acup.mp. electrostimulation OR functional electrical stimulation OR muscle OR gait)
MEDLINE via OVID	((progressive adj2 ("multiple sclerosis" or MS)).mp.) AND (exp Exercise Therapy physiotherapy.mp. OR physical therapy.mp. OR rehabilitation OR "activities of daily living" OR exercise therapy OR motion therapy, continuous passive OR muscle stretching exercises OR plyometric exercise OR resistance training OR rehabilitation, vocational OR exp Exercise Therapy OR exp Plyometric Exercise OR exercise.mp. OR exp Exercise Movement Techniques OR exp Exercise OR Electric Stimulation OR electric stimulation therapy OR electroacupuncture OR spinal cord stimulation OR transcutaneous electric nerve stimulation OR Transcutaneous Electric Nerve Stimulation OR exp Acupuncture Therapy OR exp Acupuncture Analgesia OR exp Acupuncture OR acupuncture.mp.)
Pedro	“progressive AND multiple AND sclerosis”

3.4 Results

3.4.1 Outcome of search

From the electronic search 1027 articles were identified and four articles were identified from relevant article's reference lists (Figure 3-1). Of these, 197 were duplicates leaving 834 unique publications for screening by title and abstract. After screening 783 articles were excluded. Full texts of 51 articles were read and 36 were excluded. From the remaining 15 articles; there were two instances of two papers that were from the same study but had used different outcome measures and so they were combined (Barrett et al., 2009, Esnouf et al., 2010, Patti et al., 2003, Patti et al., 2002). Thus 13 studies (published within 15 articles) were included within this review (Figure 3-1).

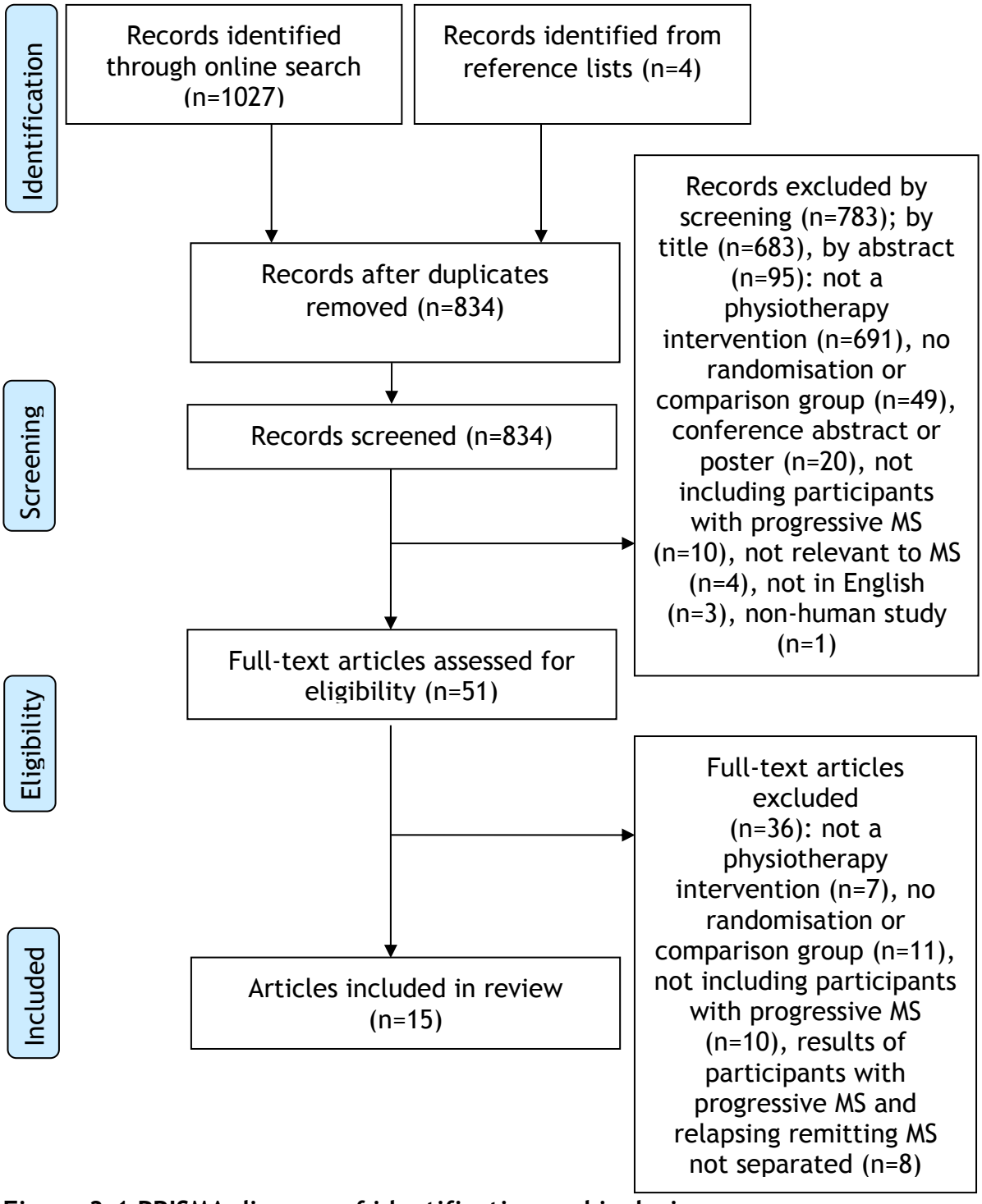

Figure 3-1 PRISMA diagram of identification and inclusion process

Abbreviations: n: number; MS: multiple sclerosis

3.4.2 Quality assessment, study design and sample characteristics

PEDro scores ranged from 5-9 out of 10 (Table 3-2). Lower scores were mainly due to lack of blinding of patients, therapists or assessors and not conducting analyses with intention to treat when appropriate. Only one article (Barrett et al., 2009) supplied a power calculation used to determine their sample size but due to 'drop outs' the results were subsequently underpowered. From the remaining studies, six highlighted their lack of power calculation (Baker et al., 2007, Briken et al., 2014, Miller et al., 2011, Paoloni et al., 2013, Skjerbaek et al., 2014, Taylor et al., 2014) and four highlighted their small sample size (Donnellan and Shanley, 2008, Giovannelli et al., 2007, Klefbeck and Hamrah Nedjad, 2003, Lo and Triche, 2008) as methodological limitations; two studies did not mention either a power calculation or comment on their sample size (Freeman et al., 1997, Patti et al., 2003, Patti et al., 2002).

From the studies included in the review there were nine randomised controlled trials (described in 11 articles) (Barrett et al., 2009, Briken et al., 2014, Donnellan and Shanley, 2008, Esnouf et al., 2010, Freeman et al., 1997, Giovannelli et al., 2007, Klefbeck and Hamrah Nedjad, 2003, Miller et al., 2011, Patti et al., 2003, Patti et al., 2002, Skjerbaek et al., 2014), two randomised trials (Paoloni et al., 2013, Taylor et al., 2014) and two randomised crossover trials (Baker et al., 2007, Lo and Triche, 2008). The length of intervention ranged from 15 days to 24 weeks and the frequency of intervention ranged from twice weekly to daily. Eight studies did not follow up participants after the intervention period (Baker et al., 2007, Barrett et al., 2009, Briken et al., 2014, Donnellan and Shanley, 2008, Esnouf et al., 2010, Freeman et al., 1997, Lo and Triche, 2008, Skjerbaek et al., 2014, Taylor et al., 2014, Patti et al., 2003, Patti et al., 2002) and four studies included a follow up assessment at 4 (Klefbeck and Hamrah Nedjad, 2003), 8 (Miller et al., 2011), 10 (Giovannelli et al., 2007) and 18 weeks (Paoloni et al., 2013) after the intervention had ended (Table 3-3).

Table 3-2 PEDro scores for included studies

Author	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	Total
Freeman et al.	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Patti et al.†	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Patti et al.†	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Klefbeck and Hamrah Nedjad	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Baker et al.	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	6
Giovanelli et al.‡	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Donnellan & Shanley	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Lo & Triche	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Barrett et al.§	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5
Esnouf et al.§	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Miller et al.	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Paoloni et al.	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Taylor et al.	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Briken et al.	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Skjerbaek et al.	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7

C1: specification of inclusion criteria (no point awarded for this criterion); C2: randomisation of participants; C3: concealment of allocation; C4: groups similar at baseline; C5: blinding of subjects; C6: blinding of therapists; C7: blinding of assessors; C8: one key outcome measure taken for at least 85% of sample; C9: intention to treat analysis if appropriate; C10: between group statistical analysis; C11: point measures and measures of variability
EC assessed all articles,(Baker et al., 2007, Barrett et al., 2009, Briken et al., 2014, Donnellan and Shanley, 2008, Esnouf et al., 2010, Freeman et al., 1997, Giovannelli et al., 2007, Klefbeck and Hamrah Nedjad, 2003, Lo and Triche, 2008, Miller et al., 2011, Paoloni et al., 2013, Patti et al., 2003, Patti et al., 2002, Skjerbaek et al., 2014, Taylor et al., 2014) LP assessed 8 articles(Baker et al., 2007, Barrett et al., 2009, Briken et al., 2014, Donnellan and Shanley, 2008, Esnouf et al., 2010, Freeman et al., 1997, Giovannelli et al., 2007, Lo and Triche, 2008) and EHC assessed 8 articles.(Giovannelli et al., 2007, Klefbeck and Hamrah Nedjad, 2003, Miller et al., 2011, Paoloni et al., 2013, Patti et al., 2003, Patti et al., 2002, Skjerbaek et al., 2014, Taylor et al., 2014)
†Patti et al. 2002 and Patti et al. 2003 described the same study.
‡All three reviewers rated this paper initially and discussed results to ensure consistency.
§ Barrett et al. 2009 and Esnouf et al. 2010 described the same study.

Table 3-3 Evidence table

Author, date and design	Sample size PPMS SPMS EDSS range Drop outs	Intervention, duration, length of session, frequency	Comparison/ control	Time Points (weeks)	Outcome measures*	Main findings*
Freeman et al.1997 *RCT*	n=66 PPMS (n=6) SPMS (n=60) EDSS 5.0-9.5 Drop out: 4 (6%)	6 weeks, MDT in-patient rehabilitation, 45 min, 2/week (n=32)	Wait list control (n=34)	0, 6	Pri: EDSS, FIM, LHS	Between group: FIM (p<0.001), LHS (p<0.01)
Patti et al. 2002 *RCT*	n= 111 PPMS (n=23) SPMS (n=88) EDSS 4-8 Drop out: 13 (12%)	12 weeks: 6 week MDT out-patient rehabilitation, 50-60 min, 6/week, followed by 6 week HEP, 60 min, 5/week (n=58)	HEP for 12 weeks (n=33)	0, 6, 12	Pri: EDSS, SF-36 Sec: BDI, SET, FIS	Between group: SF-36: RE subscale (p<0.005) all other subscales (p<0.001), BDI(p<0.001), SET (p<0.001), FIS (p<0.001)
Patti et al. 2003 *RCT*	As above	As above	As above	As above	Pri: FIM Sec: EDSS	Between group: FIM (p<0.001)
Klefbeck and Hamrah Nedjad 2003 *RCT*	n=15 progressive MS EDSS 6.5-9.5 Drop out: 1 (7%)	10 weeks: Inspiratory muscle trainer, 3 sets of 10 repetitions, twice every second day (n=7)	Normal treatment which had deep breath exercises, regular phone calls (n=8)	0, 10, 14	Pri: VC, FVC, FVC%, FEV FEV%, Max insp pressure, Max exp pressure, FSS, Borg scale	Between group: Max insp pressure (p<0.01) Within group: I: max exp pressure (p<0.02)
Baker et al. 2007 *Randomised*	n= 6 progressive MS EDSS $\geq$ 7	3 weeks: Standing frame,30 min/day (n=3) I+C swapped after 3 weeks	HEP of abdominal crunches, bridging, pelvic	0, 3, 6	Pri: Ashworth Scale, Spasm frequency, Resting ROM in supine	Between group: Resting ROM in supine: L ankle (p=0.020), R ankle (p=0.026), L hip (p=0.039), R hip (p=0.020)

crossover design	Drop out: 0 (0%)	(no washout period)	and lumbar rolls, 5 repetitions of 8 exercises (n=3)			Within group: I: Ashworth scale, R ankle (p=0.08), L ankle (p=0.08) C: spasm frequency, R leg (p=0.06)
Giovanelli et al. 2007 *RCT*	n=38 All SPMS EDSS 3-7.5 Drop out: 2 (5%)	15 days: I: BTX-A injection in either upper limb (FDS, FCU, FCR) or lower limb (tibialis posterior, gastrocnemius, soleus) followed by 40min/day of passive movements to prevent muscle contractures (n=20)	BTX-A injection only (n=28)	0, 2, 4, 12	Pri: MAS, VAS of relief from spasticity in injected muscle	Between group: MAS (p<0.01), VAS (p<0.01)
Donnellan & Shanley 2008 *RCT*	n=14 All SPMS EDSS 1.5-7.0 Drop out: 1 (7%)	5 weeks: Chinese medical acupuncture, 2/week (n=7)	Minimal acupuncture† , 5 weeks, twice a week (n=7)	0, 5	Pri: MSIS-29 phys, MSIS-29 psych Sec: FSS, GHQ-12	Between group (C vs I): MSIS-29 psych sub-score I (p=0.04)
Lo & Triche 2008 *Randomised crossover design*	n=13 PPMS (n=5) SPMS (n=8) EDSS 4.9 SD 1.2 Drop out: 0 (0%)	12 weeks: BWSTT, 3 weeks, 2/week, 40 min, followed by 6 week washout then BWSTT and robot orthotics a/a (n=6) ‡	Same as I but BWSTT and robot orthotics first (n=7)	0, 3, 9, 12	Pri: EDSS, Timed 25 foot walk, 6 min walk, DST Sec: step length ratio	Between group: DST: (p=0.06) Within group: Whole sample: timed 25 foot walk (p=0.0002), 6 min walk (p=0.002), DST (p=0.0007) and EDSS (p=0.001)
Barrett et al. 2009 *RCT*	n=53 All SPMS EDSS 4-6.5 Drop out: 7 (13%)	18 weeks, Peroneal FES, worn in daily life (n=20)	30 min HEP of trunk and pelvic stability, lower limb strength, balance, 18 weeks, 1-2/ day, (n=24)	0, 6, 12, 18	Pri: 10 m walk speed Sec: 3min walk distance	Within group: I with FES vs I without: 10 m walk speed (p=0.001), 3 min walk distance (p=0.004) C: 10 m walk speed (p=0.001) C: 3 min walk distance (p=0.005)

Esnouf et al.2010 *RCT*	n= 64 All SPMS EDSS 4-6.5 Drop out: 11 (17%)	As above (n=32)	As above (n=32)	0, 18	Pri: COPM performance and satisfaction scores, Number of falls	Between group: COPM performance (p=0.0038), satisfaction (p=0.007) Falls (p=0.036)
Miller et al. 2011 *RCT*	n= 30 PPMS (n=11) SPMS (n=19) EDSS 6.5-8 Drop out: 2 (7%)	8 weeks, Domiciliary physiotherapy, 60 min, 2/week (n=15)	Wait list control (n=15)	0, 8, 16	Pri: MSIS-29 Sec: EDSS, FIM, MSQoL, MS-RS, BPI, HADA, HADD, Dynamometry, 10 m walk, timed sit to stand	Between group: R knee extensor strength(p=0.018), L knee flexor strength (p=0.006), R knee flexor strength (p=0.001), HADA (p=0.014)
Paolini et al. 2013 *RT (3 armed trial)*	n= 42 All SPMS EDSS 2-6 Drop out: 0 (0%)	4 weeks: 3/week G1: 60 min passive movements to prevent contractures + 30 min SMV (n=14) G2: BTX-A injection 2 weeks before study then same as G1 (n=14) G3: BTX-A injection 2 weeks before study and 60 min passive movements same as G1 (n=14) §	-	0, 10, 22	Pri: MAS, FSS, Barthel index	Within group: G1: Knee MAS (p<0.001), ankle MAS (p<0.001), FSS (p=0.004) G2: Knee MAS (p<0.001), ankle MAS (p<0.001), FSS (p=0.05) G3: Knee MAS (p<0.001), ankle MAS (p<0.001), Both knee and ankle MAS higher at 22 weeks than 10 weeks (p<0.05), FSS (p=0.02), Barthel index (p=0.004)
Taylor et al. 2013 *RT*	n= 25 All SPMS EDSS 4-6.5 Drop out: 5 (20%)	24 weeks: Weeks 1-6: peroneal FES worn in daily life, Weeks 7-12: addition of gluteal FES weeks 13-18: eight sessions of core stability physiotherapy and HEP of core stability exercises,	Same as I but with physiotherapy and HEP first followed by FES (n=14)	-4, 0, 6, 12, 18, 24	Pri: ROGA, 10 m walk speed, MSIS-29, Falls frequency	Between group: ROGA: Without FES week 24 (p=0.044), with FES week 18 (p=0.028) Within group: I: MSIS-29 psych week 18 (p<0.05), MSIS-29 phys week 24 (p<0.05), 10 m walk speed with peroneal FES (p=0.06) and gluteal FES (p=0.06),

		weeks 19-24 continue with HEP, FES wear continued for second 12 weeks (n=11)				falls frequency (p<0.05) C: 10 m walk speed with FES vs no FES (p<0.05), MSIS-29 phys week 24 (p<0.05), falls frequency (p<0.05)
Briken et al. 2014 *RCT (4 armed trial)*	n= 47 PPMS (n=11) SPMS (n=31) || EDSS 4-6 Drop out: 5 (11%)	10 weeks, 15-45 min (mean Borg 4.6), 2-3/week Three groups: Arm ergometry (n=12), Rowing (n=12) and Cycling (n=12) §	Wait list control n=11	0, 10	Pri: VO_2 peak, 6 Min walk, VLMT, IDS, FIS	Between group (all vs C): Cycle group: VO_2 peak (p=0.003), 6 Min walk test (p=0.005), VLMT (p=0.009), depression (p=0.035). Arm group: 6 Min walk test (p=0.003), VLMT (p=0.007), fatigue (p=0.013), IDS (p=0.001). Rowing group: VLMT (p=0.001)
Skjerbaek et al. 2014 *RCT*	n=11 PPMS (n=3) SPMS (n=8) EDSS 6.5-8.0 Drop out: 1 (9%)	4 weeks: 10 sessions, Endurance training: predominantly UL exercises (6 x 3 min at target work rate 65-75% VO_2max with 30 – 60 sec sprints each interval) and standard in-patient rehabilitation (n=6)	Standard in-patient rehabilitation (n=5)	0, 4	Pri: VO_2 peak, MDI, MSIS-29, 9HPT, HGT, BBT, 6minWCT	Between group: VO_2 peak (p=0.06)

Abbreviations: 6minWCT: 6 minute wheelchair test, 9HPGT: 9 hole peg test, BBT: box and block test, BDI: beck depression inventory, Borg: the borg scale of perceived exertion, BPI: brief pain inventory, C: control group, COPM: Canadian occupational performance measure, DST: double-limb support time, FCR: flexor carpi radialis, FCU: flexor carpi ulnaris, FDS: flexor digitorum superficialis, FEV: Forced expiratory volume, FEV%: forced expiratory volume in percentage of FVC, FIM: functional independence measure, FIS: fatigue impact scale, FSS: fatigue severity scale, FVC: forced vital capacity, FVC%: forced vital capacity percentage predicted, GHQ-12: general health questionnaire 12, HADA: hospital anxiety and depression scale anxiety sub-scale, HADD: hospital anxiety and depression scale depression sub-scale, HEP: home exercise plan, HGT: hand grip test, HRmax: heart rate max, I: intervention group, IDS: inventory of depressive symptoms, L: left, LHS: London handicap scale, m: metre, MAS: modified ashworth scale, max exp: maximal expiratory, max insp: maximal inspiratory, MDI: major depression inventory, MDT: multi-disciplinary team, min: minutes, MSIS-29: multiple sclerosis impact scale, MSIS-29 phys: multiple sclerosis impact scale physical subscale, MSIS-29 psych: multiple sclerosis impact scale psychological subscale, MSQoL: Leeds multiple sclerosis quality of life scale, n: sample size, Pri: primary outcome measures, R: right, RCT: randomised controlled trial, RE: role functioning emotional sub-scale, ROGA: Rivermead observational gait analysis, ROM: range of motion, RT: randomised trial, Sec: secondary outcome measures, SET: Tempelaar social experience checklist, SF-36: short form 36 health survey,

SMV: segmental muscle vibration, UL: upper limb, VAS: visual analogue scale, VC: vital capacity, VLMT: verbal learning memory test, VO_2 peak: peak oxygen uptake.
*Baseline values of all outcome measures and final values/magnitude of changes can be found in table 3-4.
† Minimal acupuncture: a form of sham acupuncture where needles are inserted to a shallower depth and not at true acupuncture points (MacPherson et al., 2002).
‡ Groups did not return to baseline after 6 week washout period so analysis conducted after end of first trial.
§ Intervention group referred to as "I" throughout apart from studies by Paolini et al. and Briken et al where the three experimental arms are referred to as "G1", "G2" and "G3" and "Arm ergometry", "Rowing" and "Cycling" respectively.
|| Characteristic data of drop outs not supplied.

Six studies investigated physiotherapy as part of a multi-dimensional intervention (Freeman et al., 1997, Giovannelli et al., 2007, Paoloni et al., 2013, Patti et al., 2003, Patti et al., 2002, Skjerbaek et al., 2014, Taylor et al., 2014) and seven studies investigated the use of only a physiotherapy intervention (Baker et al., 2007, Barrett et al., 2009, Briken et al., 2014, Donnellan and Shanley, 2008, Esnouf et al., 2010, Klefbeck and Hamrah Nedjad, 2003, Lo and Triche, 2008, Miller et al., 2011). Study sample sizes ranged from 6-111 participants, EDSS scores ranged from 1.5-9.5. Eight studies included participants with both SPMS and PPMS (Baker et al., 2007, Briken et al., 2014, Freeman et al., 1997, Klefbeck and Hamrah Nedjad, 2003, Lo and Triche, 2008, Patti et al., 2003, Patti et al., 2002, Skjerbaek et al., 2014) and five studies included only participants with SPMS (Barrett et al., 2009, Donnellan and Shanley, 2008, Giovannelli et al., 2007, Paoloni et al., 2013, Taylor et al., 2014). There were no studies that included only participants with PPMS (Table 3-3). There were 45 outcome measures used across the 15 articles with few instances of commonality despite often measuring the same symptom or functional status. Baseline measurements of all outcome measures and final values or change values for the main findings of each study can be found in Table 3-4.

Table 3-4 Primary and secondary outcome measures with baseline values and main findings from each trial

Author, date and design	Outcome measures and baseline values	Main findings [Intervention, Control]
Freeman et al. 1997 *RCT*	Pri: EDSS*: I: 6.5(5.0-9.0), C: 6.5(6.0-8.5) FIM*: I: 67(13-87), C: 69.5(18-84) LHS†: I: 61.5(13), C: 66.2(8.74)	Between group (Change values): FIM*: motor domain: 4.0(-10,19), 2.5(-16,5) (p<0.001), Self-care domain: 1.5(-5,9), -1.0(-9,3) (p<0.0001) LHS†: 2.9 (8.9), -2.7 (8.6)(p<0.01)
Patti et al. 2002 *RCT*	Pri: EDSS†: I: 6.2(1.2), C: 6.1(1.2) SF-36 subscales: RE†: I: 56.1(40.4), C: 42.1(43.4), PF†: I: 39.3(23.0), C: 31.2(23.1), RP†: I: 36.9(36.2), C: 26.4(36.8), BP†: I: 58.2(26.0), C: 65.4(27.1), GH†: I: 49.9(21.1), C: 45.0(20.6), VT†: I: 47.8(17.5), C: 42.7(18.4), SF†: I: 59.8(21.5), C: 57.6(27.1), MH†: I: 54.2 (22.8), C: 53.4 (23.7) Sec: BDI†: I: 11.0(7.5), C: 12.5(7.6) SET†: I: 28.9(6.0), C: 29.3(5.9) FIS†: I: 116.8(40.9), C: 127.0(36.0)	Between group (Change values): SF-36 subscales: RE†: 6.2(23.7), -0.1(0.3) (p<0.005), PF†: 6.91(18.1), -0.1(0.3) (p<0.001), RP†: 14(24.3), -0.2(0.5) (p<0.001), BP†: 14.9(20.0), -0.1(0.6) (p<0.001), GH†: 5.8(10.5), -0.2(0.5) (p<0.001), VT†: 7.4(12.5), -0.1(0.5) (p<0.001), SF†: 11.5(14.6), -0.1(0.3) (p<0.001), MH†: 7.7(15.8), -0.1(0.5) (p<0.001) BDI†: -2.2(3.4), 0.1(1.0) (p<0.001), SET†: -2.6(6.0), -0.3(0.8)(p<0.001), FIS†: -18.8(14.3), 0.6(0.9) (p<0.001)
Patti et al. 2003 *RCT*	Pri: FIM†: I: 92.9(11.0), C: 93.7(16.4) Sec: EDSS†: I: 6.2(1.2), C: 6.1(1.2)	Between group (Change values): FIM†: 10.2(11.8): 0.0(0.7) (p<0.001)
Klefbeck and Hamrah Nedjad 2003 *RCT*	Pri: VC (L)*: I: 2.4(0.5-3.4), C: 2.1(0.5-6.2) FVC (L)*: I: 2.7(1.0-3,4), C: 2.6(1.3-6.7) FVC%*: I: 78(36-93), C: 69(38-127) FEV (L)*: I: 2.2(1.0-3.3), C: 2.3(1.3-5.0) FEV%*: I: 83(82-100), C: 88(81-100) Max insp pressure (cmH_20)*: I: 42(28-74), C: 52(15-120)	Between group (Final values): Max insp pressure*: 67(55-100),C: 54(10-126) (p<0.01) Within group (Final values): I: max exp pressure*: 63(44-80) (p<0.02)

	Max exp pressure (cmH_20)*: I: 46(36-58), C: 51(20-147) FSS*: I: 4.2(2.8-6.0), C: 5.1(2.0-6.7) Borg scale*: I: 14(9-17), C: 14(10-17)	
Baker et al. 2007 *Randomised crossover design*	Pri: Ashworth Scale*: whole sample: R hip flex: 1.5(1-3), L hip flex: 2.0(1-2), R hip abd: 1.0(1-3), L hip abd: 2.0(1-2), R knee: 1.5(2-3), L knee: 2.0(2-3), R ankle: 2.0(2-3), L ankle: 2.0(2-3) Spasm frequency*: whole sample: R: I: 2.0(0-4), L: I: 2.0(0-4) Resting ROM in supine*: whole sample: R ankle: 10(10-12), L ankle: 13.5(10-15), R knee: 2.5(0-5), L knee: 2.0(0-2), R hip: 10(0-10), L hip: 20(5-20)	Between group (Final values): Resting ROM in supine*: R ankle: 5.0(-5-7), 10(7-12) (p=0.020), L ankle: 2.5(0-7), 10(10-15) (p=0.026), R hip: 0.0(0-5), 10(5-15) (p=0.020), L hip: 5.0(0-10), 10(5-10) (p=0.039) Within group (Final values): I: Ashworth scale*: R ankle: 2.0(1-3) (p=0.08), L ankle: 1.5(1-3) (p=0.08) C: spasm frequency R leg*: 1.0(0-4) (p=0.06)
Giovanelli et al. 2007 *RCT*	Pri: MAS†: I: 3.63(0.49), C: 3.61(0.50) VAS of relief from spasticity in injected muscle, week 2: I: 5.18 (1.10), C: 5.50(1.38)	Between group (Change values): MAS†: -0.95(0.78), -0.28(0.46) (p<0.01) VAS of relief from spasticity in injected muscle†: 2.68(1.08), 1.06(1.16) (p<0.01)
Donnellan & Shanley 2008 *RCT*	Pri: MSIS-29 phys†: I: 55.2(23.6), C: 57.7(23.8) MSIS-29 psych†: I: 34.3(23.7), C: 48.4(30.0) Sec: FSS†: I: 4.6(2.4), C: 2.8(1.9) GHQ-12†: I: 15.8(9.9), C: 17.7(9.5)	Between group (Change values, C vs I): MSIS-29 psych†: 23(21.0), 6.0(13.9) (p=0.04)
Lo & Triche 2008 *Randomised crossover design*	Pri: EDSS†: whole sample: 4.9(1.2) 25 foot walk (s)†: whole sample: 9.9(4.2) 6 min walk (m)†: whole sample: 220.3(96.5) DST(%): whole sample: 33.2(8.0) Sec: step length ratio†: whole sample: 0.9(0.1)	Between group (Change values): DST†: -7.1(3.9), -1.7(3.9) (p=0.06) Within group (Change values): 25 foot walk†: 3.1(2.4) (p=0.0002) 6 min walk†: 83.4(78.0) (p=0.002)

		DST†: -5.5(4.1) (*p*=0.0007) EDSS†: -1.0(0.7) (*p*=0.001)
Barrett et al. 2009 *RCT*	Pri: 10 m walk (ms^{-1})†: I: 0.79(0.35), C: 0.68(0.28) Sec: 3 min walk (m)†: I: 99(44), C: 97(44)	Within group (Final values): I with FES vs I without: 10 m walk†: 0.80(0.35) (*p*=0.001) 3 min walk†: 125 (55) (*p*=0.004) C: 10 m walk†: 0.77(0.29) (*p*=0.001) C: 3 min walk†: 113 (46) (*p*=0.005)
Esnouf et al. 2010 *RCT*	Pri: COPM performance*: I: 3.5(1.75-5.0), C: 3.4(2.2-5.6) COPM satisfaction*: I: 2.2(1.0-5.0), C: 2.6(1.0-4.6) Number of falls: n/a	Between group (Change values): COPM performance*: 1.1(0.1-2.0), 0.0(0.0-0.9) (*p*=0.0038) COPM satisfaction*: 1.7(0.3-2.7), 0.0(0.0-1.0) (*p*=0.007) Number of falls (final values)*: 5, 18 (*p*=0.036)
Miller et al. 2011 *RCT*	Pri: MSIS-29†: I: 89.9(22.8), C: 82.8(17.3) Sec: EDSS†: I: 7(0.5), C: 7.1(8.1) FIM†: I: 68.9(12.9), C: 72.2(14.2) MSQoL†: I: 11.9(5.3), C: 8.3(5.3) MS-RS†: I: 32.7(13.9), C: 27.9(9.4) BPI†: I: 26.7(27.7), C: 25.6(17.7) HADA†: I: 6.0(5.7), C: 3.1(2.1) HADD†: I: 5.8(3.3), C: 6.3(3.6) Dynamometry (kg)†: R knee ext: I: 10.0(5.9), C: 9.3(6.0), R knee flex: I: 9.7(5.1), C: 5.5(4.3), L knee ext: I: 7.2(5.1), C: 8.4(6.7), L knee flex: I: 7.7(6.0), C: 7.5(6.8) 10 m walk (s): I: 41.2(32.9), C: 43.4(27.7) timed sit to stand (s): I: 6.2(2.3), C: 5.8(3.4)	Between group (Change values): R knee ext strength†: 11.1(6.1), 8.4(6.7) (*p*=0.018) L knee flexor strength†: 6.9(5.3), 5.0(5.6) (*p*=0.006) R knee flexor strength†: 8.7(5.7), 4.8(4.2) (*p*=0.001) HADA†: 6.2(5.0), 3.8(4.0) (*p*=0.014)
Paolini et al. 2013	Pri: Knee MAS ‡: G1: 3(3-4), G2: 4(3-4), G3: 4(3-4)	Within group (Final values): G1: Knee MAS‡: 3(2-3) (*p*<0.001)

RT (3 armed trial)	Ankle MAS‡: G1: 4(3-4), G2: 4(4-4), G3: 4(4-4) FSS§: G1: 53.6(2.31), G2: 43.4(3.10), G3: 48.5(2.77) Barthel index§: G1: 79.8(1.63), G2: 76.4(2.95), G3: 77.5(1.50)	Ankle MAS‡: 3(2-3) (p<0.001) FSS§: 46.7(2.75) (p=0.004) G2: Knee MAS‡: 3(2-3) (p<0.001) Ankle MAS‡:3(3-4) (p<0.001) FSS§: 39.7(2.97) (p=0.05) G3: Knee MAS‡: 3(2-4) (p<0.001) Ankle MAS‡: 4(3-4) (p<0.001) Knee and ankle MAS higher at 22 weeks than 10 weeks: week 10 values: Knee MAS: 3(2-3) (p<0.05), Ankle MAS: 3(3-4) (p<0.05) FSS§: 42.5(2.17)(p=0.02) Barthel index§: 77.8(1.47) (p=0.004)
Taylor et al. 2013 *RT*	Pri: ROGA without FES‡: I: 13.0(8.5-21), C: 15(11.5-17.5) 10 m walk (ms^{-1})‡: I: 0.72(047-1.31), C: 0.82(0.51-1.01) MSIS-29 phys‡: I: 48.8(30.6-55.0), C: 46.3(16.3-56.3) MSIS-29 psych‡: I: 38.8(23.6-54.2), C: 27.2(11.1-50.0) Falls frequency‡: I: 23.3(8.3-67.1), C: 9.75(1.1-50.0)	Between group (Final values): ROGA‡: Without FES week 24: 11(6-14.3), 17(14.5-20) (p=0.044), with FES week 18: 10(5.3-13), 12(10-16) (p=0.028) Within group (Final values): I: MSIS-29 phys‡: 26.3(16.2-38.1) (p<0.05), MSIS-29 psych‡: week 18: 19.4(9.7-27.3) (p<0.05) 10 m walk‡: with peroneal FES: 1.2(0.72-1.27) (p=0.06), with peroneal and gluteal FES‡: 1.04(0.76-1.27)(p=0.06) Falls frequency‡: 4(3.-7.75) (p<0.05) C: 10 m walk with peroneal and gluteal FES vs no FES‡: 0.89(0.64-1.09) (p<0.05), MSIS-29 phys‡: 35.0(21.3-51.3) (p<0.05) Falls frequency‡: 0.5(0.0-3.075) (p<0.05)
Briken et al. 2014 *RCT (4 armed trial)*	Pri:VO_2 peak (ml $O_2.min^{-1}$)†: Cycling: 1490.18(528.20), Arm ergometry: 1352.30(431.26), Rowing: 1306.00(421.79), C: 1377.40(325.19) Sec: 6 Min walk (m)†: Cycling: 288.65(99.3), Arm ergometry: 296.79(123.79), Rowing: 306.61(103.69),	Between group (Final values): Cycling vs C: VO_2 peak†: 1253.70(297.33) (p=0.003) 6 Min walk†: 344.97(118.30), 319.49(109.49) (p=0.005), VLMT†: 62. (7.18), 51.50(8.20) (p=0.009) IDS: 14.73 (9.49), 18.40(10.36) (p=0.035) Arm ergometry vs C:

	C: 325.92(117.35) VLMT†: Cycling: 52.18(6.03), Arm ergometry: 46.80(10.22), Rowing: 51.09(10.42), C: 47.50(5.91) IDS†: Cycling: 18.36(12.27), Arm ergometry: 21.10(10.24), Rowing: 13.91(7.82), C: 14.10 (7.94), FIS†: Cycling: 35.00(18.07), Arm ergometry: 45.00(14.73), Rowing: 35.27(13.86), C: 38.00(15.15)	6 Min walk†: 360.03(154.64), 319.49 (109.49) (p=0.003) VLMT†: 58.10(8.48), 51.50(8.20) (p=0.007), FIS†: 31.80(11.09), 39.30(17.49) (p=0.013), IDS†: 12.30(6.57), 18.40(10.36) (p=0.001). Rowing vs C: VLMT†: 63.09(9.94), 51.50(8.20) (p=0.001)
Skjerbaek et al. 2014 *RCT*	Pri: VO_2 peak (ml $O_2.min^{-1}$)†: I: 642(209), C: 872(386) MDI†: I: 10.6(1.7), C: 14.6(7.3) MSIS-29†: I: 86(11.9), C: 76(20.5) 9HPGT (s)†: I: 36.8(13.6), C: 66.9(61.7) HGT (N)†: I: 20.3(8.7), C: 19.9(10.3) BBT (blocks.min^{-1})†: I: 23.6(8.5), C: 27.0(8.4) 6minWCT (m)†: I: 205(136), C: 313(71)	Between group (Change values): VO_2 peak†: 308(312), 2(29) (p=0.06)

Abbreviations: 6minWCT: 6 minute wheelchair test, 9HPGT: 9 hole peg test, abd: abduction, BBT: box and block test, BDI: beck depression inventory, Borg: Borg rating of perceived exertion, BP: bodily pain, BPI: brief pain inventory, C: control group, COPM: Canadian occupational performance measure, DST: double-limb support time, ext: extensor, FEV: Forced expiratory volume, FEV%: forced expiratory volume in percentage of FVC, FIM: functional independence measure, FIS: fatigue impact scale, flex: flexion, FSS: fatigue severity scale, FVC: forced vital capacity, FVC%: forced vital capacity percentage predicted, GH: general health, GHQ-12: general health questionnaire 12, HADA: hospital anxiety and depression scale anxiety sub-scale, HADD: hospital anxiety and depression scale depression sub-scale, HGT: hand grip test, I: intervention group, IDS: inventory of depressive symptoms, L: left, LHS: London handicap scale, m: metres, MAS: modified ashworth scale, max exp: maximal expiratory, max insp: maximal inspiratory, MDI: major depression inventory, MH: mental health, min: minutes, MSIS-29: multiple sclerosis impact scale, MSIS-29 phys: multiple sclerosis impact scale physical subscale, MSIS-29 psych: multiple sclerosis impact scale psychological subscale, MSQoL: Leeds multiple sclerosis quality of life scale, PF: physical functioning, Pri: primary outcome measure, R: right, RCT: randomised controlled trial, RE: role functioning emotional, ROGA: Rivermead observational gait analysis, ROM: range of motion, RP: role physical, RT: randomised trial, s: seconds, Sec: secondary outcome measures, SET: Tempelaar social experience checklist, SF: social functioning, SF-36: short form 36 health survey, VAS: visual analogue scale, VC: vital capacity, VLMT: verbal learning memory test, VO_2 peak: peak oxygen uptake, VT: vitality.

*Values are median(range).

†Values are mean(SD).

‡Values are median(interquartile range).

§Values are mean(SE).

3.4.3 Interventions

There were four instances when the same type of intervention was implemented: physiotherapy as part of a multi-disciplinary rehabilitation intervention was investigated by two studies (Freeman et al., 1997, Patti et al., 2003, Patti et al., 2002), Functional Electrical Stimulation (FES) was investigated by two studies (Barrett et al., 2009, Esnouf et al., 2010, Taylor et al., 2014), exercise therapy was investigated by three studies (Briken et al., 2014, Miller et al., 2011, Skjerbaek et al., 2014), and a combination of botulinum toxin type A (BTX-A) injections and manual stretches was investigated by two studies (Giovannelli et al., 2007, Paoloni et al., 2013). The following interventions were investigated by one study each: acupuncture (Donnellan and Shanley, 2008); inspiratory muscle training (Klefbeck and Hamrah Nedjad, 2003); Body Weight Supported Treadmill Training (BWSTT) and robotic orthotics (Lo and Triche, 2008) and therapeutic standing using a standing frame (Baker et al., 2007).

3.4.4 Physiotherapy as part of a multi-disciplinary rehabilitation programme

The evidence is positive regarding the efficacy of a six week multi-disciplinary rehabilitation programme for the rehabilitation of people with progressive MS. The two studies (described in three articles) which used multi-disciplinary rehabilitation programmes found improvements in disability when measured using the Functional Independence Measure, however the EDSS level remained unchanged (Freeman et al., 1997, Patti et al., 2003, Patti et al., 2002). Improvements were also found in depression, social experience, quality of life and fatigue and these were maintained at six weeks post intervention (Patti et al., 2003, Patti et al., 2002) (Table 3-3). The multi-disciplinary rehabilitation programmes differed both in delivery setting and the control group interventions, however both had positive effects.

3.4.5 Functional Electrical Stimulation

The evidence is conflicting regarding the efficacy of using FES as an intervention for the rehabilitation of people with progressive MS. The two studies which used FES (described in three articles) found positive results for an orthotic effect and decrease in falls with FES in comparison to a home exercise plan aimed at improving core stability (Barrett et al., 2009, Esnouf et al., 2010, Taylor et al., 2014). However, Taylor et al. (2014) found their FES intervention produced a therapeutic effect in gait quality, while Barret et al. (2009) found only their home exercise plan produced a therapeutic effect on walking speed and endurance. These conflicting results may be due to differences in duration of the interventions, the control group interventions and the use of gluteal stimulation in addition to peroneal FES by Taylor et al (Table 3-3).

3.4.6 Exercise therapy

The evidence is inconclusive regarding the efficacy of using exercise therapy for the rehabilitation of people with progressive MS. Two of the three studies which used exercise therapy investigated endurance training in a clinical environment (Briken et al., 2014, Skjerbaek et al., 2014) and the third investigated resistance training and functional exercises in a home environment (Miller et al., 2011). The two endurance studies measured fitness and found improvements but only Briken et al. reported a significant improvement (Briken et al., 2014, Skjerbaek et al., 2014). Briken et al. (2014) also reported significant improvements in mobility, depression, fatigue and cognitive function and Miller et al. reported significant improvements in muscle strength and anxiety. There was no significant improvement in any of the other outcomes of these studies (Table 3-3). Differences in results between these studies may be due to differences in inclusion criteria and the intervention protocol. Skjerbaek et al. (2014) and Miller et al. (2011) included participants with a higher level of disability (EDSS 6.5-8.0) while Briken et al. (2014) included participants with a moderate disability (EDSS 4.0-6.0). Skjerbaek et al. (2014) and Briken et al. (2014) conducted their final assessments at four and six weeks respectively without a

follow up assessment while Miller et al. did a follow up assessment eight weeks after their eight week intervention (Table 3-3).

3.4.7 Botulinum toxin type A injections and manual stretches

The evidence in this review is positive regarding the efficacy of using a combination of BTX-A injections and manual stretches for the rehabilitation of people with progressive MS. However, it is unclear which combination is the most effective. The two studies which used BTX-A injections and manual stretches differed as Giovannelli et al. (2007) compared BTX-A injections to BTX-A injections and manual stretches whilst Paoloni et al. (2013) conducted a three arm randomised trial investigating different combinations of BTX-A injections, manual stretches and segmental muscle vibration (Table 3-3). Each group experienced improvements in spasticity, with those who only received BTX-A injections experiencing the least improvement (Giovannelli et al., 2007). Significant improvements were also found in subjective relief of symptoms (Giovannelli et al., 2007), fatigue and activities of daily living (Paoloni et al., 2013) in those who received a combination of BTX-A injections and manual stretches, however improvements in spasticity were not maintained at 18 weeks post intervention compared to six weeks post intervention (Paoloni et al., 2013). In contrast, interventions incorporating segmental muscle vibration also produced significant improvements in spasticity however these improvements were maintained at follow up assessments (Paoloni et al., 2013) (Table 3-3).

3.4.8 Acupuncture

The evidence is inconclusive regarding the efficacy of acupuncture for the rehabilitation of people with progressive MS. There was only one study that investigated Chinese Medical acupuncture in comparison to minimal acupuncture (Donnellan and Shanley, 2008) (a form of sham acupuncture where needles are inserted to a shallower depth and not at true acupuncture points (MacPherson et al., 2002)). Minimal acupuncture produced significant improvements in the

psychological sub-score of the Multiple Sclerosis Impact Scale compared to Chinese Medical acupuncture. No changes were seen in any other outcomes (Table 3-3).

3.4.9 Inspiratory muscle training

The evidence in this review is positive regarding the efficacy of using inspiratory muscle training for the rehabilitation of people with progressive MS, although only one study was found which investigated this technique. The study investigated the use of an inspiratory muscle trainer in comparison to deep breathing exercises (Klefbeck and Hamrah Nedjad, 2003). A significant improvement was found in maximal inspiratory pressure and maximal expiratory pressure in those using the inspiratory muscle trainer. No changes were seen in any other outcomes (Table 3-3).

3.4.10 Body Weight Supported Treadmill Training and robotic orthotics

The evidence in this review is inconclusive regarding the efficacy of BWSTT and robotic orthotics for the rehabilitation of people with progressive MS. Only one study investigated BWSTT compared to BWSTT and robotic orthotics in a randomised crossover trial (Lo and Triche, 2008). There was a trend towards improvement in double-limb support time in those receiving BWSTT compared to those receiving BWSTT and robotic orthotics. At the end of the study, all participants showed significant improvements in walking speed, endurance, double limb support time and disability but not in step length ratio (Table 3-3). However, after the washout period, values had not returned to baseline. Therefore between group analyses were performed after the initial three week intervention period.

3.4.11 Therapeutic standing

Similar to other physiotherapeutic interventions only one study investigated the efficacy of therapeutic standing for the rehabilitation of people with progressive MS. The use of a standing frame was compared to a daily home exercise programme consisting of abdominal crunches, hip rolls, lumbar rolls and bridging (Baker et al., 2007). Therapeutic standing produced significant improvements in passive hip and ankle range of motion and a trend towards improvement in ankle spasticity; while the home exercise programme resulted in trends towards improvement in frequency of leg spasms (Table 3-3).

3.4.12 Overall outcome of studies

Generally the articles presented a positive effect of physiotherapy for the rehabilitation of people with progressive MS. Thirteen studies (described in 15 articles) found that the intervention group improved more than the comparison or control group in at least one outcome measure (Baker et al., 2007, Barrett et al., 2009, Briken et al., 2014, Esnouf et al., 2010, Freeman et al., 1997, Giovannelli et al., 2007, Klefbeck and Hamrah Nedjad, 2003, Miller et al., 2011, Patti et al., 2003, Patti et al., 2002, Skjerbaek et al., 2014). One study only found statistically significant improvements in within group analysis (Paoloni et al., 2013), one study reported that neither group made an improvement large enough for statistical significance (Skjerbaek et al., 2014) and one study found that participants who received the control treatment improved more than those who received the intervention (Donnellan and Shanley, 2008). It is important to note that only one study used a power calculation to determine the required sample size however due to ‘drop outs’ the results were subsequently underpowered.

3.4.13 Clinical significance of improvements

From the papers included in this review, where a statistically significant change in the outcome measure was reported data detailing minimal clinically important differences (MCID) in people with MS was sought. Only four outcome measures had MCID data available; the timed 25 foot walk test (improvement of 17.2%) (Coleman et al., 2012), the six minute walk test (improvement of 21.6 m) (Baert et al., 2014), the fatigue impact scale (improvement of 10-20 points) (Rendas-Baum et al., 2010) and the physical sub-score of the multiple sclerosis impact scale (improvement of 8 points) (Costelloe et al., 2007b). Four studies had statistically significant results that used at least one of these outcome measures (Table 3-5) (Briken et al., 2014, Lo and Triche, 2008, Patti et al., 2002, Taylor et al., 2014). All of these results were above the level of MCID for people with MS indicating a positive perspective for using physiotherapy in the rehabilitation of people with progressive MS. The four trials used four different interventions; multidisciplinary rehabilitation (Patti et al., 2002), FES (Taylor et al., 2014), exercise therapy (Briken et al., 2014) and BWSTT and robotic orthotics (Lo and Triche, 2008). Three trials included participants who were moderately affected by MS (EDSS levels 4-6.5) (Briken et al., 2014, Lo and Triche, 2008, Taylor et al., 2014) and one had a wider range and included those more severely affected (EDSS levels 4-8) (Patti et al., 2002) (Table 3-5). Two of the studies used the fatigue impact scale (Briken et al., 2014, Patti et al., 2002), both produced similar levels of change despite Patti et al. (2002) including participants with a wider EDSS range and higher levels of fatigue at baseline. Similarly, two studies used the six minute walk test (Briken et al., 2014, Lo and Triche, 2008), both produced similar improvements despite differences in distance walked at baseline.

Table 3-5 Statistically significant results of outcome measures with available data of MCID for people with MS

Author EDSS	Intervention	Outcome Measure (MCID)	Baseline values	Change values/ Final values
Patti et al. 4-8	MDT out-patient rehabilitation	FIS (10-20 points)	**I:** 116.8 (40.9) **C:** 127.0 (36.0)	**I:** -18.8 (14.3)* **C:** 0.6 (0.9)* (*p*<0.001)†
Taylor et al. 4-6.5	FES	MSIS-29 physical sub-score (8 points)	**I:** 48.8(30.6-55.0) **C:** 46.3(16.3-56.3)	**I:** 26.3(16.2-38.1)‡ (*p*<0.05)§ **C:** 35.0(21.3-51.3)‡ (*p*<0.05) §
Briken et al. 4-6	Exercise therapy	6minWT (21.6 m) FIS (10-20 points)	**Cycling:** 288.65 m (99.3) **Arm:** 296.79 m (123.79) **Rowing:** 306.61 m (103.69) **C:** 325.92 m (117.35) **Cycling:** 35.00(18.07) **Arm:** 45.00(14.73) **Rowing:** 35.27(13.86) **C:** 38.00(15.15)	**Cycling:** 344.97(118.30)‡ **C**: 319.49(109.49)‡ (*p*=0.005)† **Arm:** 360.03(154.64)‡ **C:** 319.49 (109.49)‡ (*p*=0.003)† **Arm:** 31.80(11.09)‡ **C:** 39.30(17.49)‡ (*p*=0.013)†
Lo & Triche Mean 4.9 (SD 1.2)	BWSTT and robot orthotics	T25fWT (17.2%)|| 6minWT (21.6 m)	**whole sample:** 9.9 s (4.2) **whole sample:** 220.3 m (96.5)	**whole sample:** -3.1(2.4)* (*p*=0.0002)§ **whole sample:** 83.4(78.0)* (*p*=0.002)§

Abbreviations: 6minWT: six minute walk test, Arm: arm ergometry group, C: control group, FIS: fatigue impact scale (maximum score: 160), I: intervention group, MCID: minimal clinically importance difference, MDT: multi-disciplinary, MSIS-29: multiple sclerosis impact scale (maximal physical sub-score: 80), T25fWT: timed 25 foot walk test
All baseline and change/final values are mean (SD)
*Change values
† Between group analysis
‡ Final values
§ Within group analysis
||17.2% improvement is a change in speed.[35] Lo & Triche presented results in seconds.[32] Means of baseline and change in speed calculated from raw time data equated to a 40% improvement in speed.

3.5 Discussion

Overall the evidence presented in this review is positive regarding the efficacy of physiotherapy for the rehabilitation of people with progressive MS although it should be noted that the evidence is generally weak due to the variation in interventions and a lack of power within studies.

The Progressive MS Alliance, and previous reviews, have highlighted that research regarding progressive MS and higher levels of disability is an area requiring further work (Fox et al., 2012, Hogan and Coote, 2009, Toomey and Coote, 2012). Only four studies within the review included participants with a high level of disability (EDSS $\geq$ 6.5) (n=62), five studies did not make a distinction in the level of disability of their participants (n=242) and four studies included only participants with a mild to moderate level of disability (EDSS $\leq$ 6.0) (n=178). Exercise therapy was the only intervention where the effects were compared across disability levels (Giovannelli et al., 2007, Miller et al., 2011, Paoloni et al., 2013). The results of these studies agreed with those of previously published reviews which found exercise therapy produced improvements in fatigue in those with a mild to moderate disability (Andreasen et al., 2011), while no significant results were found in those with a higher level of disability (Dalgas et al., 2008).

The results of this review were consistent with those found in systematic reviews of the other interventions for either MS or similar patient groups. Previously published reviews investigating the efficacy of physiotherapy interventions for people with MS found that multi-disciplinary rehabilitation programmes increased participation (as a result of a decrease in disability) and quality of life (Khan et al., 2007); were unable to draw a conclusion as to the effectiveness of acupuncture (Karpatkin et al., 2014); found respiratory muscle trainers increased maximal inspiratory and expiratory pressure (Martin-Valero et al., 2014) and that BWSTT and BWSTT with robotic orthotics both improved walking speed, double-limb support time, endurance and step length ratio (Swinnen et al., 2012). However there was no improvement in step length ratio in the study presented in this review. Two reviews assessing the efficacy of FES in chronic stroke found it had a good orthotic effect (Kottink et al., 2004) but were unable

to conclude on the efficacy of a therapeutic effect (Pereira et al., 2012). Reviews assessing interventions for neurological impairments were unable to ascertain the most effective adjunct therapy to BTX-A injections in the treatment of spasticity (Kinnear et al., 2014) and that therapeutic standing produced improvements in ankle range of motion (Newman and Barker, 2012). However, the similarity between the results of this review and other reviews for the same interventions in similar patient groups such as RRMS should be approached with caution due to the previously mentioned methodological weaknesses in the body of evidence presented.

Symptom management and rehabilitation is one of the five key research priorities identified by the Progressive MS Alliance (Fox et al., 2012). However, impact on quality of life and participation should also be a consideration. Thus, identifying the patient groups who would experience the greatest improvement in clinical outcomes to particular interventions, with the greatest impact upon quality of life and participation, would help establish the full effectiveness of interventions.

3.5.1 Study limitations

This review was limited to only include articles in published in English. It was further limited by the broad spectrum of physiotherapy as a discipline which led to variation in duration, dose, intensity and the type of interventions included.

3.5.2 Future Work

Future work should be carried out to investigate physiotherapy interventions for people with progressive MS using adequately powered randomised trials with an appropriate control, long term follow up and adequate reporting (Hoffmann et al., 2014). Studies should, where possible, aim to use a core set of outcome measures (Paul et al., 2014) and use outcome measures for which there is available data of MCID for people with MS. Future research should also consider

participants with PPMS and SPMS separately to investigate whether this has an effect on clinical outcomes. Further investigation is recommended to ascertain which patient groups would experience largest improvements in quality of life from improvements in clinical outcomes.

3.6 Conclusion

In conclusion, the evidence within this review demonstrates that physiotherapy may be effective in the rehabilitation of people with progressive MS. This review which focussed on people with progressive MS had similar findings to reviews in similar patient groups. Further investigation, with appropriately powered studies and consistency in outcome measures between studies is required to strengthen this evidence base and conduct meta-analyses of the evidence.

3.7 Articles published since systematic search was carried out

A second search carried out in November 2017 found four more articles which met the inclusion criteria. Two (Briken et al., 2016, Geertz et al., 2015) were sub-analyses of an RCT already included in the review (Briken et al., 2014), and two were new RCTs (Pilutti et al., 2016, Straudi et al., 2016).

Both of the sub-analyses of Briken et al. (2014) combined data from all three exercise groups (arm ergometry, rowing and cycling) and compared this against the waitlist control group. When examining the effect on participation in physical activity, Geertz et al. (2015) found that the exercising group progressed positively along the trans-theoretical change model (p=0.016) and improved self-efficacy (p=0.014) while the control group regressed and decreased respectively (Table 3-6). Briken et al. (2016), found that while nine weeks of training produced an increase in the amount of brain derived neurotrophic factor in serum after exercise, there was no effect on resting levels (Table 3-6). The limitations of the original RCT were discussed earlier. There may also be an

additional limitation involved in combining the exercise groups because, in the original RCT, the individual groups displayed different changes in both physiological outcomes, such as VO_2max, and psychological outcomes, such as depression (Table 3-3). Despite this potential for sample bias, there was no justification in either of the sub-analyses for combining the groups. In summary, while these sub-analyses produce positive results and strengthen the case for using exercise for the rehabilitation for people with progressive MS, the evidence overall remains inconclusive. The limitations of the evidence were discussed in section 3.4.6.

Both Pilutti et al. (2016) and Straudi et al. (2016) conducted RCTs that involved BWSTT. Pilutti et al. (2016) compare an intervention of recumbent stepping to BWSTT and Straudi et al. (2016) compared BWSTT with robotic orthotics to conventional gait training. Straudi et al. (2016) provided a power calculation while Pilutti et al. (2016) did not, and both trials included participants with a higher EDSS score (Table 3-6).

As their primary outcome measure, Pilutti et al. (2016) found that both their groups enjoyed the intervention, be it BWSTT or recumbent stepping, but the recumbent stepping group had a larger effect size. They also found that both groups improved their fatigue scores in the physical and psychosocial dimensions of the Modified Fatigue Impact Scale (Table 3-6).

Straudi et al. (2016) found that the BWSTT with robotic orthotics group increased their walking endurance, measured by the Six Minute Walk Test, by a non-clinically significant amount at three weeks (16.94m SD 18.96, $p<0.05$) and by a clinically significant amount at six weeks (23.22m SD 32.33, $p<0.01$). An improvement was also reported in gait speed at three weeks (0.05 m/s SD 0.13 $p<0.05$), but this was not maintained post intervention. The BWSTT with robotic orthotics group also displayed a greater improvement in the Mental Health component of the SF-36 at three weeks, but this was not maintained at six or 12 weeks. The BWSTT with robotic orthotics group improved their balance at both three and six weeks, and in quality of life in relation to vitality at six weeks, social function at three and six weeks, mental health at six and 12 weeks, health perception at six weeks and the mental summary component of the Short form 36 at six weeks. The conventional gait training group showed improvements in

quality of life in relation to pain at three weeks, and mental health at six weeks (Table 3-6).

Both of these trials are linked to the study by Lo and Triche (2008) that compared BWSTT to BWSTT with robot orthotics. Lo and Triche (2008) found improvements in both groups in disability, walking speed and endurance. These are similar to the results by Straudi et al. (2016). Quality of life was not measured by Lo and Triche (2008) but was by the two new trials. Straudi et al. (2016) reported an improvement in quality of life in within group analyses but Pilutti et al. (2016) reported no change in quality of life. In summary these three studies indicate positive evidence for the use of BWSTT for the rehabilitation of people with progressive MS, for improving gait speed and walking endurance in those who are severely affected. The effect of BWSTT on quality of life is inconclusive, and further investigation into this is warranted.

These four publications add to the existing body of work in the systematic review in sections 3.1-3.6, however the overall conclusions of the review remain the same. This is because even though both of the new RCTs focussed on participants with higher levels of disability, and both produced positive results in rehabilitation, they shared a methodological weakness with the previous body of work that neither had a sample size that was statistically powered. Overall, these new studies further strengthen the evidence for the efficacy in using physiotherapy for the rehabilitation of people with progressive MS but that larger fully powered studies are still required. In particular, these new studies strengthen the evidence for the use of BWSTT. It was positive that, per the recommendations of the original review, both new trials involved more disabled participants and that one RCT was powered.

Table 3-6 Evidence table of studies published since original search

Author, date and design	Sample size PPMS SPMS EDSS range Drop outs	Intervention, duration, length of session, frequency	Comparison/ control	Time Points (weeks)	Outcome measures	Main findings
Geertz et al 2015 Sub analysis of Briken et al 2014	n=47 PPMS (n=31)* SPMS (n=11) EDSS 4.0-6.0 Drop out: 5 (11%)	10 weeks, 15-45 min (mean Borg 4.6), 2-3/week: training either arm ergometry, rowing or cycling (n=32)	Wait list control (n=10)	0, 10	PA levels, stage of TTM, self-efficacy, perceived PA barriers, exercise specific social support	BG ex vs waitlist: TTM: ex progressed and control regressed (p=0.016) Self-efficacy: increase in ex group and decrease in control (p=0.014)
Briken et al. 2016 Sub analysis of Briken et al 2014	n=47 PPMS (n=31)* SPMS (n=11) EDSS 4.0-6.0 Drop out: 5 (11%)	10 weeks, 15-45 min (mean Borg 4.6), 2-3/week: training either arm ergometry, rowing or cycling (n=32)	Wait list control (n=10)	0, 10	Resting and post ex serum concentrations of Irisin, BDNF, Interleukin-6	Post ex increase in BDNF in ex group (p<0.01)
Pilutti et al 2016 *RCT*	n=12 PPMS (n=4)* SPMS (n=6) EDSS 6.0 -8.0 Drop out: 2 (17%)	12 weeks 3/week, 30 min sessions recumbent stepping (n=5)	12 weeks 3/week, 30 min sessions BWSTT (n=5)	0, 12	Pri: Participant experience of training Sec: MSFC, MFIS, HRQOL	Both groups enjoyed training, recumbent stepping had larger ES in post ex feeling, Both groups improved physical and psychosocial fatigue (p=0.04, p=0.01)*
Straudi et al 2016	n=58 PPMS (n=16)* SPMS (n=36) EDSS 6.0-7.0 Drop out: 6	6 weeks, 2/week, up to 60 min sessions BWSTT with robot orthotics (n=27)	6 weeks, 2/week, 60 min sessions of CGT: lower limb stretching,	0, 3, 6, 12	10MWT, 6MinWT, BBS, TUG, FSS, PHQ-9, SF-36	BG: (BWSTT vs CGT) 10mWT: 3 wks: 0.05 m/s SD 0.13 (p<0.05) 6minWT:3 wks: 16.94m SD 18.96, (p<0.05), 6 wks: 23.22m SD 32.33

(10%)	strengthening, balance and gait exercises (n=25)	(*p*<0.01) WG^(all *p*<0.05): BWSTT: BBS: 3 wks, 6 wks SF-36 vitality: 6 wks SF-46 social function 3, 6 wks SF-36 Mental health; 12 wks CGT: SF-36: 3, 6 wks

Abbreviations: 10mWT: 10 metre walk test, 6minWT: 6 minute walk test; BG: between group differences; BBS: Berg Balance Scale; BWSTT: body weight supported treadmill training; CGT: conventional gait training; ES: effect size; FSS: Fatigue Severity Scale; MSQOL: Multiple Sclerosis Quality of Life-54; MSFC: Multiple Sclerosis Functional Composite; MFIS: Modified Fatigue Impact Scale; PHQ-9; Patient Health Questionnaire; Pri: primary outcome measure; Sec: secondary outcome measures; SF-36: Short Form 36; TTM: transtheoretical model of change; TUG: Timed Up and Go test; WG: within group differences

*Demographic data not supplied on drop outs

^Size of change not reported.

Chapter 4 Survey of clinical services for people with Multiple Sclerosis in the UK – Rationale and Methods

There is a lack of available pharmacological treatments for decreasing disease activity in those with progressive forms of MS, and thus treatment often focuses on symptomatic management and rehabilitation. Physiotherapy has a positive impact on the management of MS, and rehabilitation has been recognised as a research priority for progressive MS (Fox et al., 2012). The current National Institute for Health and Care Excellence (NICE) guidelines and Healthcare Improvement Scotland clinical standards for Neurological Health Services, state that everyone with MS in the UK should have access to an MS Specialist, physiotherapy, and receive a comprehensive annual review. This review can be carried out by any member of the MS team, does not have to be conducted in a clinical environment, and should cover all aspects of care including medication, symptom management, disease course, general health, participation and social care needs (NICE, 2014b, Healthcare Improvement Scotland, 2009). However, it is unknown at this time how often people with progressive MS receive a regular review or what the level of access is to clinical services.

This chapter will outline the rationale and methods for an online survey of people with progressive Multiple Sclerosis (MS), in the United Kingdom (UK), exploring the access, use and views of MS clinical services. The online survey was conducted, between August and September 2015, using the UK MS register, a national register which is a longitudinal research database. Due to the lack of treatments available for people with progressive forms of MS and a lack of distinction between MS types in previous research this study recruited only people with primary and secondary progressive MS. This study has been published across two articles (Campbell et al. 2017. Access, delivery and perceived efficacy of physiotherapy and use of complementary and alternative therapies by people with progressive multiple sclerosis in the United Kingdom: An online survey. Multiple Sclerosis & Related Disorders, 12, 64-69. (Appendix 2) Campbell et al. 2017. Access and Use of Clinical Services and Disease-Modifying Therapies by People with Progressive Multiple Sclerosis in the United Kingdom. International Journal of MS Care, 19, 275-282. (Appendix 3)) the results of which are combined in Chapter 5.

4.1 Evidence base of access, use and opinion of Multiple Sclerosis clinical services

4.1.1 Definition of access and use

Access to services is a multi-faceted concept. In the past, access was simply defined as the entry into the care of, or use of, a health care system (Clark, 1983). However, access is in fact, more complex. Access can be related to the availability of services, the adequate supply of services and the opportunity to enter into said services (Levesque et al., 2013). Furthermore there is a difference between having access to a service, and gaining access which is measured in utilisation (Gulliford et al., 2002). Access can be broken down into several dimensions and determinants. These include not just the availability of services, but the opportunity to be able to use them, the utilisation of services, and organisational barriers which may affect a person's ability to be able to gain access such as waiting times, distance to travel and affordability (Levesque et al., 2013).

This study explored two aspects of access. The first was the opportunity to be able to enter into a service regardless of external factors such waiting times and transport issues. This was defined as 'access'. Secondly the utilisation of services was explored. This was defined as 'use' (Levesque et al., 2013).

4.1.2 Access and use of Multiple Sclerosis clinical services in the United Kingdom

Four studies have previously explored access and use of clinical services by people with MS in the UK. Two of these were published after this present survey was conducted. These were the 'Generating Evidence in Multiple Sclerosis Services' (GEMSS) by the MS Trust (Mynors et al., 2015) and the 'My MS My Needs survey' by the MS Society (MS Society, 2016c)

The GEMMS study examined the access and use of MS Services, over a four year period between 2012 and 2015, among people with MS across 10 sites in England

and two in Scotland from MS Nurses' active caseloads (Mynors et al., 2015). A return rate of 47% from 2,648 paper surveys produced a sample of 1,254. The researchers found that the most commonly consulted practitioner was the MS Specialist Nurse with 77% of respondents reporting that they had consulted a MS Nurse recently for their MS. However, this study may have been biased, as participants were recruited from MS Specialist Nurse active caseloads. While the average MS Nurse's caseload was described as having 46% of patients with an Expanded Disability Status Scores (EDSS) of 5.5 or below, 38% between 6.0 and 7.5 and 16% of 8.0 or above, the EDSS of the respondents was not described. Furthermore there was no distinction made between participants with progressive MS and those with Relapsing Remitting MS (RRMS).

The 'My MS My Needs survey' by the MS Society, used a combination of postal surveys and the UK MS Register to maximise response rate (MS Society, 2016c). They used 30% online and 70% postal surveys, 10,888 people were recruited with all types of MS from Scotland, Northern Ireland, England and Wales. As well as examining employment, use of social benefits and co-ordination of care, the study explored access to Disease Modifying Therapies (DMTs), rehabilitation therapies and access and use of services. The study found that 86% of respondents had access to an MS Specialist (Neurologist or Nurse). They also found that 56% of the cohort were taking DMTs, 17% did not have access to a physiotherapist, 32% of physiotherapy was provided from non-NHS sources and that the majority (74%) of all MS Services were delivered in a clinical setting (MS Society, 2016b). While these results provide a valuable insight into the access and use of services across the UK the results were not separated by MS type. Thus it remained unknown whether people with progressive MS have a different level of access to services and if they attend similar clinical services to those with RRMS.

A study in Northern Ireland investigated access and use of services and medications taken via interviews with 149 people with MS (EDSS 0-9.0) (MacLurg et al., 2005). The sample consisted of people with RRMS (44%) and progressive MS (56%) recruited from a network of 30 General Practitioner (GP) practices that were representative of Northern Ireland. The results indicated that irrespective of disability, access to physiotherapy services was the most common unmet need

and that use of multiple medications was directly linked to level of disability (MacLurg et al., 2005).

Edmonds et al. (2007) used qualitative methods to explore unmet needs in relation MS services in people severely affected by MS (EDSS >8.0) in Southeast London. The sample comprised 23 people with MS and 17 carers, with seven people with MS were too disabled to take part in the semi-structured interviews. Overall, both participants with MS and their carers had a poor perception of services, citing a lack in continuity of clinicians and being unable to get an appointment with clinicians when needed, despite the service existing (Edmonds et al. 2007).

In summary, the two studies which were published after this present survey, had the largest cohorts and surveyed the largest geographical areas suggested access to clinical services, especially MS Specialists, was quite high (MS Society, 2016c, Mynors et al., 2015)). However the two studies with smaller sample sizes, which had either more than half of their sample with progressive MS or focused on those with a severe disability, found that access to services was either poor or cited organisational barriers to using the service (Edmonds et al., 2007, MacLurg et al., 2005). As neither of the more recent studies focused on progressive MS this left a gap in the literature regarding the level of access to, and use of, clinical services by people with progressive MS in the UK.

4.1.3 Access and use of Multiple Sclerosis clinical services outside the United Kingdom

There have been five studies conducted outside the UK examining access and use of clinical services by people with MS. Lonergan et al. (2015) asked participants, in the Republic of Ireland, to complete a questionnaire either in person or by phone. A 51% response rate, from 632 potential participants identified from a prevalence study by the same group of researchers (Lonergan et al., 2011), generated a sample of 325, 50% of whom had a progressive form of MS (86% EDSS $\leq$ 6.0 or less, 14% EDSS > 6.0 or more). The researchers explored the perceived needs of these participants in both rural (Wexford and Donegal) and urban (Dublin) regions of Ireland with participants reporting a lack of access to

physiotherapy, particularly in those who lived rurally and had progressive MS (Lonergan et al., 2015).

A Europe wide study consisted of interviews with 137 people with MS across five countries: Belgium, Estonia, Greece, Italy and the UK (Kersten et al., 2000). The researchers did not report type of MS or EDSS score, but reported that 39% were wheelchair bound, 36% were significantly handicapped but ambulatory and 21% had no significant handicap. The participants reported that the most utilised clinicians were GP (75%), physiotherapist (57%), MS Doctor or Nurse (53%) and Occupational Therapist (28%). When the data for the UK (n=37) was isolated the most consulted clinicians were the same but in a different order: GP (95%), MS Doctor or Nurse (84%), Physiotherapist (62%) and Occupational Therapist (62%) indicating a higher rate of use of specialist Doctors and Nurses than the other countries.

A group of Swedish researchers carried out a survey of patients of one outpatients rehabilitation centre in Stockholm (Ytterberg et al., 2008). They received completed questionnaires from 219 people with MS, of whom 42% had either Primary Progressive MS (PPMS) or Secondary Progressive MS (SPMS). Respondents were predominantly mildly affected by MS with 60% having an EDSS score of 3.5 or less, 17% were moderately affected (EDSS score of 4.0-5.5) and 23.5% were severely affected (EDSS score of 6.0-9.5). The participants did not report any unmet needs in access to outpatient clinical services. However, this study only examined the service provision of one outpatient clinic and this limits the generalisability of the results. The patient perception of services is described later with similar studies in section 4.1.5.

Most recently, two qualitative studies by the same research group examined the perceived needs of people severely affected by MS in Germany, from both the patient and the health professional's perspective (Galushko et al., 2014, Golla et al., 2012). Fifteen people with MS were recruited (mean EDSS = 7.0), seven of which had a progressive form of MS (Galushko et al., 2014). In interviews all participants reported difficulty in utilising services, reporting high waiting times, lack of home community-based care and poor quality disabled access at clinics (Galushko et al., 2014). Clinicians (n=23) were recruited from four clinics, one of which was rural, and data was collected using face-to-face interviews and focus groups (Golla et al., 2012). Neurologists identified the biggest unmet need as a

lack of ability to access services due to disability, even though a service was available, while Nurses identified unmet needs mainly relating to maintaining participation and social support (Golla et al., 2012). However the results of this study should be interpreted with caution due to the small sample size. Furthermore, the purposive recruitment of patients may have led to sample bias.

In summary, studies carried out exploring access to clinical services outside the UK have been conducted only in Europe. Methodology and sample population have varied as have results creating heterogeneity in the literature. In Ireland and central Europe access to MS clinical services was poor apart from access to GPs. In contrast, access to services in Sweden was high yet this study was heavily open to bias as it only surveyed one outpatient clinic.

4.1.4 Perception of Multiple Sclerosis services in the United Kingdom

Only one study has explored patient perception of MS services in the UK. Markwick et al. (2014) reported on the service user opinion of MS services. The opinions, of 757 people with MS, were obtained from a service audit of MS services in England and Wales (Royal College of Physicians and MS Trust, 2008). The type of MS was not reported, yet 86% reported that their MS either had a "moderate" or "major" impact on their life. Predominantly the views on physiotherapy provision were negative. The most common negative comments were lack of availability of services, long waiting times, and poor flexibility in service delivery.

4.1.5 Perception of Multiple Sclerosis services outside the United Kingdom

As was described in section 4.1.3., Ytterberg et al. (2008) also explored participant's perception of services received at a clinic in Sweden. Participants were asked to rate the service on a five point Likert scale which was then dichotomised into satisfied (1-2 on scale) and dissatisfied with service (3-5 on scale). Results demonstrated that Nurses were held in the highest regard, with

96% reporting that they felt their needs were met, and 88% felt satisfied with services provided by physiotherapists. While this is a positive result this does indicate that 12% were not satisfied with physiotherapy services.

A similar study carried out by Holmoy et al. (2012) in Norway, asked 339 people with MS regarding satisfaction with services after a four week in-patient stay at a rehabilitation centre in Hakakdal. A response rate of 82% was achieved resulting in a return of 277 questionnaires. The questionnaire consisted of simple closed ended questions with categorical yes or no answers. Ninety-two percent of respondents reported that they were satisfied with the therapeutic services they received. The researchers however, unusually, did not report any demographical information on the participants.

A third Scandinavian study investigated the views of patients following a single physiotherapy session in an outpatient clinic in Norway (Normann et al., 2012). The study achieved a high response rate of 89% resulting in a sample of 64 participants. While type of MS of the participants was not reported, 77% were reported as fully ambulatory, 11% used a walking aid and 12% were using a wheelchair. The researchers reported that the participants only had positive comments on the single physiotherapy session received.

The three Scandinavian studies (Holmoy et al., 2012, Normann et al., 2012, Ytterberg et al., 2008), all reported positive patient perception of MS services, and specifically physiotherapy. Despite this, all three studies are limited in their generalisability as they recruited participants from individual sites leaving their results open to sample bias and demographics were not always reported.

4.1.6 Use of complementary and alternative therapies by people with Multiple Sclerosis

As well as medical care, people with MS often utilise Complementary and Alternative Therapies (CAT) in their own management of their MS (Bowling and Stewart, 2003). There has been some research carried out outside of the UK examining the use of CAT in people with MS but not in the UK.

Apel et al. (2006) conducted 254 semi-structured interviews, with people with MS in Germany, exploring their use of CAT in respect to frequency and therapies used. They found that 67% of their sample was currently using a CAT. The most commonly used CAT were exercise (73%), vitamins (40%), other supplements (34%), herbal medicine (25%), relaxation (25%), and massage (13%). In a follow up study exploring CAT use and disease progression, the authors noted that people with MS were more likely to use CAT in the early stages of their disease as, soon after diagnosis, people with MS are more likely to try as many therapeutic avenues as possible (Kochs et al., 2014).

In the United States of America, Stoll et al. (2012) surveyed 133 people with MS about their use of therapies other than DMTs, which included CAT. Their 13 question survey had closed, single and multiple choice answers. The authors reported that 58% of their sample had used a CAT in the prior 30 days. The most commonly used CAT were massage (30%), psychotherapy (20%), and acupuncture (13%).

Skovgaard et al. (2012) conducted an online survey of 6,455 members of MS Societies of the five Nordic countries exploring CAT use in the past year. The authors found that overall use of CAT varied slightly across the five countries with 46% of the sample having used CAT in Sweden, 52% in Denmark, 53% in Norway, 56% in Finland, and 59% in Iceland. In Denmark the most common used CAT were supplements (80%), acupuncture (16%), herbal medicine (12%), reflexology (11%), and yoga (11%). In Norway the most commonly used CAT were supplements (67%), herbal medicine (19%), acupuncture (15%), yoga (9%), and meditation (9%). In Sweden the most commonly used CAT were supplements (59%), yoga (15%), acupuncture (12%), herbal medicine (11%), and meditation (11%). In Finland the most commonly used CAT were supplements (80%), yoga (8%), acupuncture (7%), herbal medicine (6%), and meditation (6%). Lastly, the most commonly used CAT in Iceland were supplements (58%), yoga (23%), acupuncture (21%), meditation (14%), and herbal medicine (13%).

A study conducted at an outpatient clinic in Turkey surveyed 101 people with MS asking them about knowledge of, and use of CAT (Gedizlioglu et al., 2015). The researchers reported that 32% had knowledge of CAT and that 26% had used CAT

at some point, but only 6% were currently using CAT. The type of CAT used was not reported.

In summary the use of CAT by people with MS outside of the UK is high across western countries. However, in Turkey the use of CAT was significantly lower but this could have been linked to a lack of knowledge of CAT due to cultural factors. The most commonly used CAT varied from country to country but the most common in all of the research was supplements, herbal medicine, exercise, acupuncture and massage. However, despite all of this previous research exploring the use of CAT in people with MS, there was no sample solely of people with progressive MS and the data was not presented by MS type. Furthermore, there is no data available on the use of CAT by people with MS in the UK.

4.2 Summary of evidence

There has been some previous research examining access and use of clinical services in the UK but this has not been explored by MS type. Reported results have been conflicting; in the larger studies access was reported to be high while in the smaller studies, which had a larger proportion of people with progressive MS or higher disability, a lack of access was reported. Outwith the UK, access to services was poor in central Europe and Ireland yet high in Sweden. However, the results from the Swedish study were from one rehabilitation centre.

Only one study to date has examined perception of services by people with MS in the UK, from which perceptions were predominantly negative; while in Scandinavia patient perception of services was high. However, both studies focussed on single centres. This leaves a gap in the literature regarding access to, use of, and opinion of clinical services by people with progressive MS in the UK. In addition the current level of CAT use by people with progressive MS also remains unknown.

4.3 Objectives and study design

The objectives of this study were to, in relation to people with progressive MS in the UK:

- investigate the levels of access to MS Specialists, a regular review, and use of clinical services
- investigate the levels of access to, delivery of, barriers to access, and opinion of physiotherapy services by people with progressive MS in the UK
- investigate the use of CAT in the UK

A cross-sectional design was chosen as this was an exploratory study seeking to describe the current delivery and use of MS clinical services by people with progressive MS in the UK. As this was the first study of its kind in the UK there were no hypotheses posed.

4.3.1 Research Questions

In relation to access and use of MS Specialists and clinical services:

- What proportion of respondents have access to an MS Specialist and which clinical services are used for their MS?
- What proportion of respondents receive a regular review for their MS and how is this delivered?
- What proportion of respondents have ever taken and are currently taking DMTs?

Are there associations between:

- Access to and use of MS specialists and quality of life, impact of MS, type of MS, DMTs use?
- Location and access to MS specialists?
- If participants had utilised more than one clinician for their MS in the past three months and quality of life/impact of MS?
- Past and present DMTs use and quality of life/impact of MS?
- Type of MS and quality of life/impact of MS?

In relation to access and delivery of physiotherapy:

- What proportion of respondents have access to physiotherapy and how many are currently receiving physiotherapy for their MS?
- Who is the provider of physiotherapy and what is the referral process?
- How is physiotherapy delivered and what is the expected waiting time for an appointment?
- Which physiotherapy interventions have respondents received in the past three months?
- What is the respondents' perceived efficacy of physiotherapy and interventions received?

Are there associations between:

- Access to and use of physiotherapy and quality of life/impact of MS, type of MS, perceived efficacy, age, gender?
- Perceived efficacy of physiotherapy and quality of life/impact of MS, type of MS, age, gender?

In relation to preferred delivery of physiotherapy:

- Do respondents want more physiotherapy than they currently receive?
- What is the preferred delivery of physiotherapy?
- What are the most common and greatest barriers to receiving physiotherapy?

In relation to use of CAT:

- What proportion of respondents use CAT?
- Which CAT are used for respondents' MS?

Are there associations between:

- Complementary and alternative therapy use and quality of life/impact of MS, age, gender, type of MS, access to MS services, receiving a regular review, use of clinical services for their MS, and DMTs use (past and present)?

4.4 UK MS Register

The UK MS Register is a longitudinal research database funded by the MS Society since 2011. Adults with MS become members by signing up to the register online and then answer, via an online portal, regular self-report outcome measures, update demographic information and complete regular and one-off online surveys (Jones et al., 2014a). The purpose of the UK MS Register is to increase the epidemiological knowledge base of MS by collating and combining data from three sources: data collected directly from people with MS, from routine administrative data sources and from NHS clinical information systems (Ford et al., 2012). At the time of this study the data were not yet linked up with NHS clinical data therefore diagnosis of MS was self-reported.

Previous published research carried out on the register has been predominantly conducted by the research group responsible for the inception and management of the UK MS Register. Published research has included studies examining anxiety and depression (Jones et al., 2012), quality of life (Jones et al., 2013a), the impact of MS (Jones et al., 2013b) and the relationship between disability and depression (Jones et al., 2014b).

4.5 Definitions of access and use in online survey

As was discussed in section 4.2.1 access to services is a multi-faceted concept (Levesque et al., 2013). The first aspect of access explored by this study was the opportunity to be able to enter into a service regardless of external factors, defined as ‘access’. The second aspect explored was the utilisation of services, defined as ‘use’.

These terms were not explicitly explained to the respondents, however the meaning was implied in the questions asked. For example “Which of the following clinicians could you see if you wanted to?” implied the opportunity to be able to enter into a service and “Which of the following clinicians have you seen in the past three months for your MS?” implied the utilisation of a service.

4.6 Ethical approval

Ethical approval was obtained from the University of Glasgow College of Medical, Veterinary and Life Sciences Ethics Committee. The information governance panel of the UK MS Register also reviewed the protocol and approved the study. The UK MS Register had its own ethical approval from the NHS (South West - Central Bristol Research Ethics Committee, Ref: 11/SW/0160).

4.7 Inclusion criteria, identification and recruitment of respondents

Participants were considered eligible for inclusion if they were aged 18 years or older, had a progressive form of MS and were a member of the UK MS register. Potential participants were identified by the UK MS Register and were emailed informing them of the study on the 18th of August 2015. The potential participants were sent a reminder follow up email one calendar month later. Both emails contained a short description of the survey, the reasons for conducting it and a statement informing the respondent that they were under no obligation to take part and that they were free to stop completing the survey at any point. If, after this, the respondent began the survey then this was regarded as informed consent.

When this study was carried out in 2015 there were 11,041 people on the register with 4,384 of those being classed as active members on the register in the prior six months. Of the total 11,041 registrants there were 2,538 who self-reported as having a progressive form of MS. Awareness was also raised via the MS Society's website, and via a knowledge exchange event.

4.8 The online survey

An online survey via the UK MS Register was chosen as a data collection method as it provided access to a large potential cohort that would not have been feasible if data were collected using face to face interviews or survey methods. The survey comprised three sections. The first was concerned with access and

current delivery of physiotherapy; the respondent's perceived efficacy of physiotherapy and interventions received. In the second section participants were asked about their preferred delivery and potential barriers to receiving physiotherapy. The third section asked about access and use of MS Specialist and clinical services, past and present use of DMTs and use of complementary and alternative therapies.

The survey was made up of a mixture of single answer and multiple response options. Closed ended categorical questions were used to make it easier for people with cognitive impairment to complete. The survey was not developed from a pre-existing questionnaire. A validated questionnaire was not necessary as the survey was not used to accumulate a score and many of the research questions had descriptive answers, for example, the level of access to a physiotherapist. The full survey complete with logical progressions can be found in Appendix 4.

4.8.1 Survey data collection: access to Multiple Sclerosis specialist services and use of clinical services, disease modifying therapies and complementary and alternative therapies

The respondents were asked if they had access to an MS Specialist service and which clinical services they had used for their MS in the prior three months. An MS Specialist service was defined as a clinician with MS Specialist skills. If a participant did not have access to an MS Specialist service they were asked what clinical services they could access and then which they had used in the previous three months for their MS. Respondents were then asked if they received a regular review for their MS; how often that review took place; who normally undertook the review; and where the review normally took place. Previous and current use of DMTs was explored before lastly asking about if participants had recently used CAT for their MS and what type of CAT they had used.

4.8.2 Survey data collection: physiotherapy access, delivery, and perceived efficacy

Respondents were asked if they were currently receiving physiotherapy, if they had access to physiotherapy, what the route of referral was, and who was their physiotherapy provider. Respondents were then asked their perceived efficacy of physiotherapy as a discipline for their MS, which physiotherapy interventions they had received in the prior three months (for their MS) and their perceived efficacy of these interventions. Perceived efficacy was rated on a five point Likert scale: 'very harmful', 'harmful', 'neither harmful nor beneficial', 'beneficial', and 'very beneficial'. The Likert scale was used since it gave a graded categorical variable and allowed for the level of perceived efficacy to be assessed.

Respondents were then asked about the delivery of their physiotherapy. This was in terms of regularity of appointments, expected waiting times, frequency of appointments, length of appointments, the number of people usually present and where respondents normally received their physiotherapy.

4.8.3 Survey data collection: desired delivery of physiotherapy

Finally respondents were asked if they were happy with the level of physiotherapy they were currently receiving and how they would like their physiotherapy to be delivered. They were asked if they wanted more physiotherapy, how often they would like to receive physiotherapy, how long they would like their sessions to last, where they would like to receive treatment, and how many people they would like to be present. In addition the respondents were asked what barriers they encountered in receiving physiotherapy and of these, which three were the most pertinent barriers.

4.9 Routinely collected data supplied by the UK MS Register

The UK MS Register supplied demographic data, EQ-5D-3L index, Multiple Sclerosis Impact Scale-29 (MSIS-29) version 2 psychological and physical sub-scale scores and Lower Super Output Area codes or Super Output Area codes depending on location.

The EQ-5D-3L index and MSIS-29 version 2 were included as they were routinely collected by the UK MS Register and are valid self-report measures of quality of life and disease impact in people with MS. The Lower Super Output Area codes and Super Output Area codes were requested as additional information from the MS Register as these allowed geographical data to be generated.

4.9.1 Demographic data

For each participant the following demographic data were supplied by UK MS Register: age, type of MS (SPMS or PPMS only), time since diagnosis, gender and country of residence.

4.9.2 EQ-5D-3L

The EQ-5D-3L is a self-report measure of quality of life. There are five dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. For each dimension the user chooses either: “no problem at all”, “some problems”, or “severe problems”. A combination of each answer to the dimensions creates a code (for example 13223) and an index is generated depending on the relative indexes for the relevant country (EuroQol, 1990). This index ranges from -1 to 1, a higher index indicating better quality of life. Generally as an individual gets older their index will fall. For example an individual in England who is healthy and aged 60 years will have an index of approximately 0.8 whilst and individual who is 25 and healthy will have an index of 1 (Devlin et al., 2016).

4.9.3 Multiple Sclerosis Impact Scale - 29 version 2

The MSIS-29 version 2 is a 29 item self-report measure of disease impact with sub-scales in relation to the physical and psychological impact of MS and was discussed in section 2.6.3. A higher score indicates a greater impact of disease. Each question has 4 options on a Likert scale and the participant is asked to give their responses in relation to the previous two weeks (Hobart et al., 2001). These are 'not at all', 'a little', 'moderately' and 'extremely' and are scored 1-4 respectively. The original version of the MSIS-29, which had five options instead of four, was updated in 2009. The MSIS-29 is divided into two sections: the first 20 questions concern the physical impact of MS and the final 9 questions the psychological impact of MS. Physical and psychological impact sub-scales scores can range from 20-80 and 9-36 respectively (Hobart and Cano, 2009).

The physical sub-scale of the MSIS-29 version 1 was found to correlate moderately with EDSS (r= 0.63), with correlation increasing with higher scores (higher physical impact) (Gray et al., 2009) and being sensitive to change when compared to the EDSS (McGuigan and Hutchinson, 2004). Minimal important clinical difference in the physical subscale of MSIS-29 version 1 has been reported as a change of 7 points for those with an EDSS of 0.0 – 0.5 and a change of 8 for those with an EDSS of 5.5 - 8.0 (Costelloe et al., 2007a). In the psychological sub-scale a decrease of 6 or more is deemed to be clinically significant (Widener and Allen, 2014). However, there is no available minimal important clinical difference data for the physical or psychological sub-scales used in MSIS-29 version 2.

4.9.4 Lower Super Output Area codes and Super Output Area codes

Lower Super Output Area codes are geographical codes in England and Wales, generated from a post code, which provide a location within a set area and population density. Using these codes and other linked codes created by the Office for National Statistics, it is possible to convert the Lower Super Output Area code into further information such as local authority area, population

density, strategic health authority, and NHS health board (Office for National Statistics, 2016). The code is not exact enough to identify where a person lives in the same way a postcode can, but it does provide information such as the neighbourhood. Super Output Area codes are similar codes produced by the Scottish Office for National Statistics and these can be used to establish the same information in a similar manner (Scottish Office for National Statistics, 2016).

Using the Lower Super Output Area codes and Super Output Area codes the population density of where the respondent lived was generated. Using the definitions supplied by Department for Communities and Local government a settlement with a population of more than 10,000 was classified as urban and less than 10,000 was classified as rural (Department for Communities and Local Govenment, 2006).

4.10 Data collection, access and storage

The data were anonymised at an individual level using the Secure Anonymised Information Linkage system of the MS Register (Ford et al., 2009). The anonymised data were then accessed remotely, using a secure RSA SecurID™ token, on a remote desktop with no ability to download data to a local computer. Only data specific to this project was on this desktop and it was not possible to download the data to the local computer. Data and results from analysis could be requested for release, but would only be so, after they were assessed for anonymity by the Health and Information Research Unit of the UK MS Register.

4.11 Statistical analysis and handling of data

IBM SPSS Statistics version 22 was used for all statistical analysis. Percentages of total respondents to each question were calculated. Where appropriate, answers from different questions on the same subject were combined. This allowed for new variables to be created such as separating those who had used only a single service for their MS and those who had used multiple services. For example the

research question ‘Which clinical services are used for their MS?’ required answers from questions 1.1, 3.3a, and 3.3c (see below) to be answered fully.

1.1 Do you receive physiotherapy at the moment?

3.3a What other health care professionals have you seen for your MS in the past 3 months?

3.3c What other health care professionals would you be able to see for your MS if you wanted to?

A full list of research questions that required answers from multiple survey questions can be seen in Appendix 5.

Due to website programming some participants were able to answer three follow up questions about a regular review despite having said that they were not offered one. These answers (n=8) were subsequently removed. Only data relating to delivery of reviews was reported and analysed from respondents who reported receiving a review.

Data were tested for normality using Kolmogrov-Smirnov tests. All data were not normally distributed therefore Mann-Whitney tests were used to test for differences in continuous variables within sub-groups with two options, for example: EQ-5D-3L index in those who did and did not have access to physiotherapy. Kruskal-Wallis tests were used to test for differences in continuous variables in sub-groups with more than two variables, for example MSIS-29 version 2 physical subscale in participants who thought physiotherapy was ‘very beneficial’, ‘beneficial’, ‘neither beneficial or harmful’, ‘harmful’ or ‘very harmful’. Chi-square tests were used to test for independence between categorical variables. Statistical level of significance was set at $p<0.05$, and to limit the chance of type 1 errors, Bonferroni adjustments were used as appropriate.

Chapter 5 Survey of clinical services for people with Multiple Sclerosis in the UK – Results

An online survey of people with progressive Multiple Sclerosis (MS) was conducted via the UK MS Register in 2015. The main objective was to explore access and use of clinical services, in particular MS Specialists and physiotherapy, by people with progressive MS in the United Kingdom (UK). This chapter will present the results of the survey with regards to access and use of MS clinical services, delivery, desired delivery and perceived efficacy of physiotherapy and use of Complementary and Alternative Therapies (CAT). Finally the associations between access and use of clinical services and routinely collected data from the UK MS Register will be explored.

5.1 Demographics and population

There were 2,538 members of the UK MS Register who self-reported as having a progressive form of MS. A response rate of 51% produced a sample of 1,298 people with progressive MS. Not every participant had complete demographic data available, for example country of domicile. The mean age of respondents was 59 years (SD 8) with a mean Time Since Diagnosis (TSD) of 16 years (SD 9). The majority of participants, 79%, lived in England, 10% lived in Scotland, 8% in Wales and 2% in Northern Ireland. The majority of respondents were female with a female to male ratio of3:2 ; similarly the majority of respondents were diagnosed with Primary Progressive MS (PPMS) (ratio of PPMS to Secondary Progressive MS (SPMS) was also 3:2). The EQ-5D-3L index of the whole cohort was 0.49 (SD 0.2), the mean physical sub-scale score of the Multiple Sclerosis Impact Scale-29 (MSIS-29) was 56 (SD 12.6) and the mean psychological sub-scale score was 20 (SD 6.1) (Table 5-1). Mean time between survey completion and most recent completion of EQ-5D-3L and MSIS-29, which are meant to be completed quarterly, was 39 (SD 120) days and 19 (SD 111) days respectively.

There were statistically significant differences, after Bonferroni adjustment, between those with PPMS and SPMS in terms of age, TSD, gender, EQ-5D-3L index and MSIS-29 physical and psychological sub-scale scores. Compared to the

respondents with SPMS those who had PPMS were older (p<0.001), had a shorter TSD (p<0.001), had a higher EQ-5D-3L index (better quality of life) (p=0.001), a lower MSIS-29 psychological sub-scale score (p=0.004) and lower physical sub-scale score (p=0.002) (Table 5-1). More females had SPMS and PPMS (n=578, n=246 respectively) compared to males (n=234, n=240 respectively) (p<0.001). There were no statistically significant differences in MS type depending on country of residence (p=0.343) or urban/rural dwelling (p=0.219) (Table 5-1).

Table 5-1 Demographics of participants

	Whole cohort	PPMS (n=486)	SPMS (n=812)	*p*
Age (years) (n=1298)	59 (8)	60 (697.28)	59 (620.9)	p<0.001*
TSD (years) (n=1298)	16 (9)	9 (440.98)	18 (737.15)	p<0.001*
Gender n=(1298)				
Female	824 (63%)	246 (51%)	578 (71%)	p<0.001^{+}
Male	474 (37%)	240 (49%)	234 (29%)	
Country of residence	(n=1285)	(n=448)	(n=807)	
Scotland	130 (10%)	57 (12%)	73 (9%)	p=0.343
England	1030 (79%)	372 (77%)	658 (81%)	
Wales	104 (8%)	40 (8%)	64 (8%)	
N. Ireland	21 (2%)	9 (2%)	12 (2%)	
Population density	(n=1250)	(n=463)	(n=787)	
Urban living	862 (69)	329 (71%)	533 (68%)	p=0.219
Rural living	388 (31)	134 (29%)	254 (32%)	
EQ-5D-3L index	0.490 (0.20)	0.566 (677.51)	0.503 (662.66)	p<0.001*
MSIS-29 - psych	20 (6.1)	18 (601.64)	20 (662.66)	p=0.004*
MSIS-29 - phys	56 (12.6)	55 (604.47)	58 (672.45)	p=0.002*

Abbreviations: PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; TSD: time since diagnosis; MSIS-29 psych: Multiple Sclerosis Impact Scale 29 psychological sub-scale; MSIS-29 phys: Multiple Sclerosis Impact Scale 29 physical sub-scale
Figures for age, TSD, EQ-5D-3L index and MSIS-29 sub-scale scores are expressed as mean and standard deviation for the whole cohort and as median and mean rank for PPMS and SPMS.
* Statistically significant from Mann-Whitney testing after Bonferroni adjustment (0.05/5=0.01).
+ Statistically significant from Chi square testing after Bonferroni adjustment (0.05/3=0.02).

5.2 Descriptive results

5.2.1 Access to Multiple Sclerosis specialists and clinical service use

Due to a programming error responses regarding the health professions respondents consulted for their MS, MS Specialist Doctor and MS Specialist Nurse were combined and were reported as one variable 'MS Specialist'. Thus, 95% (n=1,184) of respondents reported that they had access to an MS specialist and 81% of those with access reported that they could access their MS Specialist if needed. Overall access to MS Specialists was high and varied slightly throughout the Strategic Health Authorities of England and the other three countries of the United Kingdom from 92% in East Midlands and Yorkshire & Humber to 98% in Wales (Figure 3-1).

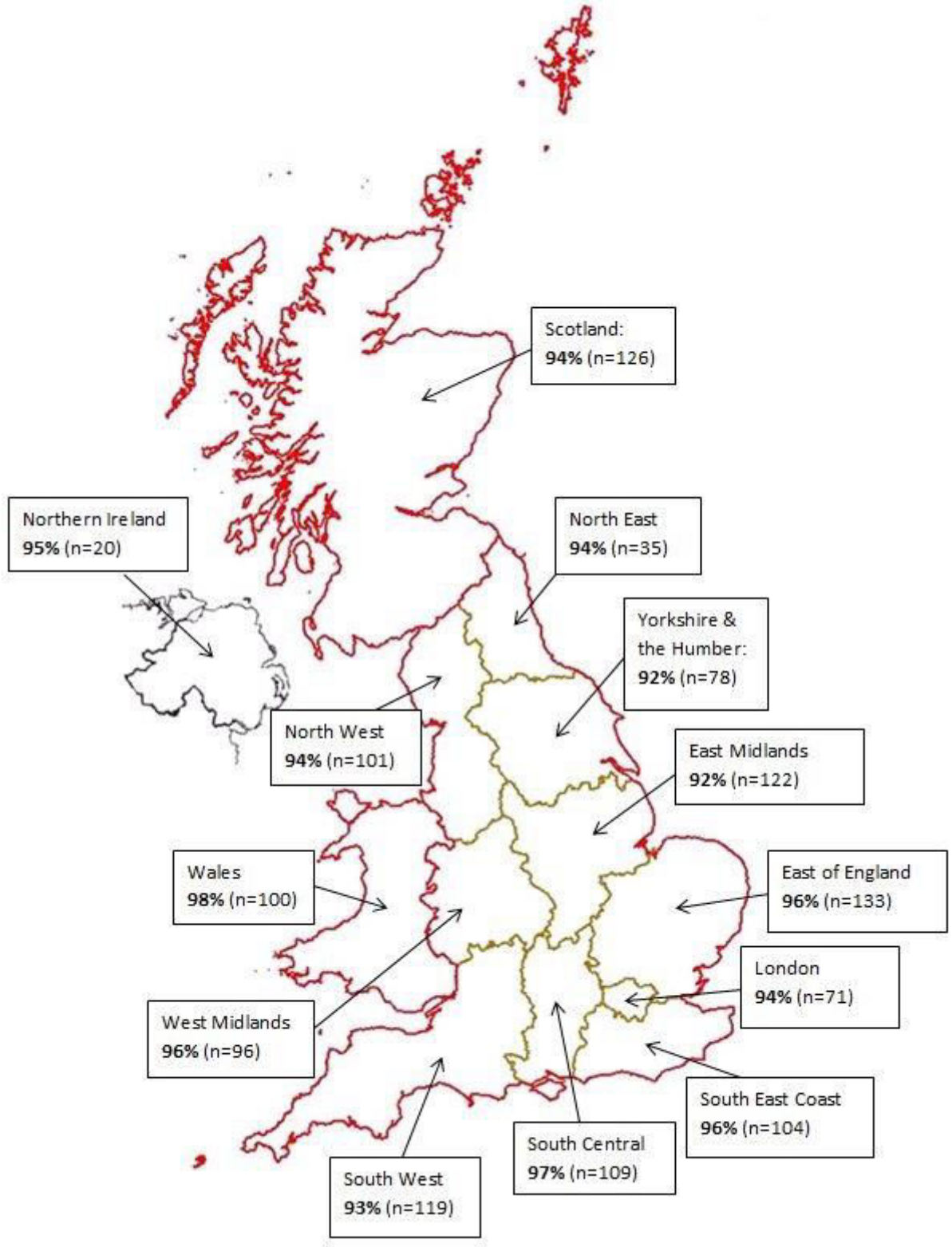

Figure 5-1 Access to MS specialists by Strategic Health Authority in England, and the other three countries of the United Kingdom

Map generated from the Office of National Statistics open geography portal in April 2016 (http://geoportal.statistics.gov.uk/)

In total 82% (n=1046) of participants had used a clinical service for their MS in the prior three months. The most used services were MS Doctor/Nurse (50%), General Practitioner (45%) and Physiotherapist (32%) (Figure 5-2).

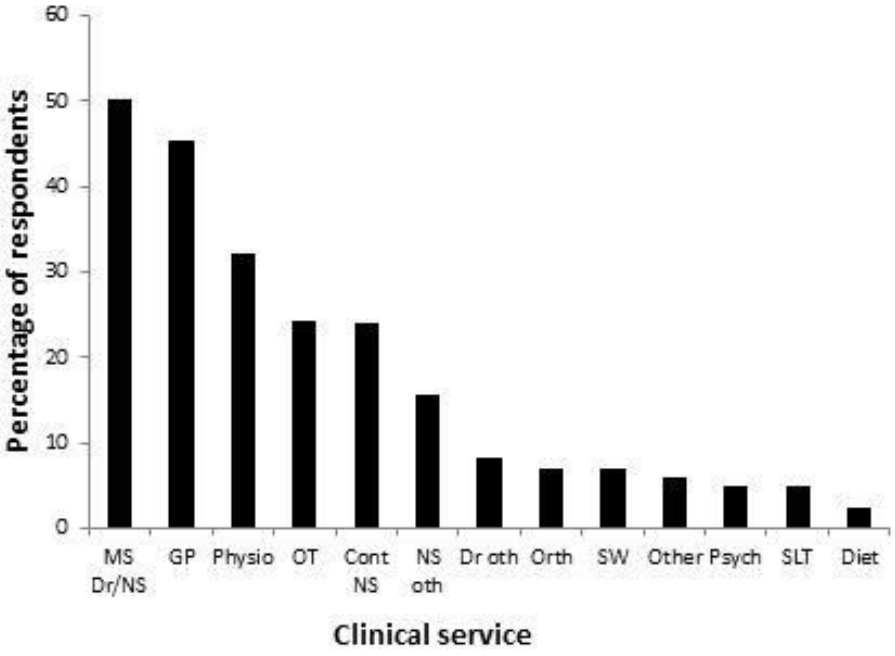

Figure 5-2 Clinical services used for MS in the past three months

Abbreviations: MSDr/NS: MS Doctor or MS Nurse; Physio: Physiotherapist; OT: Occupational Therapist; Cont NS: Continence Nurse; NS oth: Nurse other; Dr oth: Doctor other; Orth: Orthotist; SW: Social Worker; Oth: other; Psych: Psychologist; SLT: Speech and Language Therapist; Diet: Dietician

Seventy four percent (n=917) of respondents reported that they received a regular review, while 23% (n=287) reported they did not and 3% (n=39) did not know if they received a review or not. The most common frequency of the review was once a year (55%, n=505) but 37% received their review less than once a year. The most common practitioners to carry out the review was the MS Doctor (63%, n=569) or Nurse (27%, n=248) and 90% (n=819) reported that the setting for their review was in a hospital or clinic (Table 5-2).

Table 5-2 Receipt and delivery of annual review for progressive MS

Variable	n	Option	n	%
Receives regular review	1243	Yes	917	74
		No	287	23
		Don't know	39	3
Frequency of review	912	Twice a year	57	6
		Once a year	505	55
		Less than once a year	341	37
		Don't know	9	1
Clinician who delivers review	911	MS Specialist Doctor	569	63
		Nurse	248	27
		The person can vary	58	6
		Physiotherapist	12	1
		Occupational therapist	6	1
		GP	8	1
		Other*	10	1
Setting of review	911	In a hospital or clinic	819	90
		At home	43	5
		GP surgery	20	2
		Other^	19	2
		In a community centre	10	1

Abbreviations: n: number of respondents; MS: multiple sclerosis; GP: general practitioner
* Answers reported as other for who delivers review: unknown (n=5), support worker (n=1), "rehabilitation team" (n=2), "MS worker" (n=1), health administrator (n=1)
^ Answers reporter as other for setting of review: charity centre (n=12), "NHNN" (definition not provided by respondent) (n=1), unknown (n=6)

Twenty percent (n=88) of respondents were currently taking DMTs (Table 5-3). The most common DMTs participants reported taking was Beta-interferon (39%, n=34) (Table 5-4). Previous use of DMTs was reported in 24% of respondents (n=303) (Table 5-3), similarly Beta-interferon was the most commonly prescribed DMTs (Table 5-4).

Table 5-3 Past and present use of disease modifying therapies

		n	%
Present DMTs use (n=447)	Yes	88	20
	No	359	80
Past DMTs use (n=1241)	Yes	303	24
	No	938	76

Abbreviations: n: number of respondents; DMTs: disease modifying therapies

Table 5-4 Disease modifying therapies taken currently and in the past

	Current DMTs taken (n=88)		Past DMTs taken (n=303)	
	n	%	n	%
Beta-interferon (Rebif, Avonex, Betaferon)	34	39	232	77
Glatiramer acetate (Copaxone)	5	6	73	24
Dimethyl fumarate (Tecfidera)	17	19	17	6
Teriflunomide (Aubagio)	0	0	1	<1
Natalizumab (Tysabri, Antigren)	19	22	34	11
Fingolimod (Gilenya, Novartis)	11	13	15	5
Mitoxantrone (Novantrone)	2	2	31	10
Alemtuzumab (Lemtrada)	2	2	6	2

Abbreviations: DMTs: disease modifying therapies; n: number of respondents
Respondents were able to select more than one option, thus total percentages could add up to greater than 100%.

5.2.2 Physiotherapy, access, delivery and perceived efficacy

In total, 87% (n=1118) of respondents reported having access to physiotherapy and 32% (n=414) were currently receiving physiotherapy for their MS. The most common routes of referral for physiotherapy were via the MS nurse (43%), self-referral (38%) and via the General Practitioner (32%) (Table 5-5). The majority of physiotherapy was delivered on a one to one basis (80%) and most participants received their physiotherapy regularly (60%) as opposed to varying depending on symptoms (40%). When asked to select an expected waiting time for a physiotherapy appointment there was not a clearly most common selection. Six percent expected to be seen within a week and ten percent expected to wait longer than 12 weeks. Respondent selection for the other four options in

between ranged from 19-22%. The most common frequency of appointments was once or more per week (55%) and the typical length of physiotherapy appointments was 30-60 minutes (Table 5-6). The three most common providers of physiotherapy were the NHS (78%), private practice (20%) and charity (third sector) (16%) (Table 5-5). This was reflected in the setting of physiotherapy delivery, as the most common settings were in a hospital or clinical environment (46%), at home (25%) or in a charity centre (24%) (Table 5-6).

Table 5-5 Access and provider of physiotherapy

Variable	Total n	Options	n	%
Access to physiotherapy	1291	Yes	1118	87
		No	173	13
Currently receiving physiotherapy	1287	Yes	414	32
		No	873	68
Referral route	1158	MS specialist doctor/neurologist	310	27
		GP	366	32
		Self-referral	445	38
		MS specialist nurse	493	43
		Other	140	12
		Don't know	8	1
Physiotherapy provider	1106	National Health Service	859	78
		Private (self-funded)	219	20
		Private (insurance)	21	2
		Charity	187	16
		Other*	14	2

Abbreviations: n: number of respondents; MS: multiple sclerosis; GP: general practitioner.
For some questions participants were able to select more than one option.
*Providers named as 'other' included: MS registered trainer (n=1), family member or carer (n=3), self-treat (n=2), selected other but did not give details (n=8)

Table 5-6 Delivery of physiotherapy

Variable	Total n	Options	n	%
Setting of physiotherapy	461	In a hospital or clinic	210	46
		At home	116	25
		In a charity centre	110	24
		In a community centre	31	7
		Other*	51	11
Number of people present	457	1 (individual session)	366	80
		2-4	42	9
		5 or more	81	18
		Receive physiotherapy by telephone or online	5	1
Pattern of appointments	451	Regularly	270	60
		Varies depending on symptoms	181	40
Expected waiting time	192	< 1 weeks	12	6
		≥ 1 < 2 weeks	42	22
		≥ 2 < 4 weeks	36	19
		≥ 4 < 6 weeks	41	21
		≥ 6 < 12 weeks	41	21
		≥ 12 weeks	20	10
Frequency of appointments	252	Once or more a week	138	55
		Once a fortnight	46	18
		Once every 1 to 3 months	53	21
		Twice a year	10	4
		Once a year or less	5	2
Usual length of appointments	462	<30 minutes	120	26
		30 - 60 minutes	299	65
		>60 minutes	43	9

Abbreviations: n: number of respondents.
*Setting of delivery named as 'other' included: private clinic (n=25), leisure centre/gym (n=14), hydrotherapy pool (n=5), care home (n=1), at work (n=1), not specified (n=5)

The three most commonly received physiotherapy interventions in the prior three months were: a home exercise programme (83%), supervised exercise (71%) and advice or education received from a physiotherapist (65%) (Table 5-7).

Table 5-7 Physiotherapy interventions received for Multiple Sclerosis in the past three months

Intervention (total n=452)	n	%
Home exercise programme	373	83
Exercises with a physiotherapist	320	71
Advice or education	293	65
Functional electrical stimulation	110	24
Standing frame or tilt table	78	17
Acupuncture	43	10
Transcutaneous electrical stimulation	30	7
Hydrotherapy	8	2
Manual therapy	5	1
Walking aid prescription	3	<1
Whole body vibration	2	<1
Hand physiotherapy	1	<1
Women's health physiotherapy	1	<1
Joint consultation with orthoptist and physiotherapist	1	<1

Abbreviations: n: number of respondents

A total of 70% of participants reported that they thought physiotherapy was either 'beneficial' or 'very beneficial' to them in relation to their MS. Twenty-seven percent thought that it was 'neither beneficial nor harmful' and 3% thought that it was either 'harmful' or 'very harmful' for them (Table 5-8).

Table 5-8 Perceived efficacy of physiotherapy for the participant's MS

Perceived efficacy (n=1208)	n	%
Very harmful	11	<1
Harmful	20	2
Neither harmful nor beneficial	328	27
Beneficial	523	43
Very beneficial	326	27

Abbreviations: n: number of respondents

The perceived efficacy of interventions received by participants for their MS was predominantly positive with most respondents feeling that their interventions

were either 'beneficial' or 'very beneficial' for their MS. Only two interventions, acupuncture and Transcutaneous Electrical Nerve Stimulation (TENS) had more than 5% of participants report a perceived efficacy that was either 'harmful' or 'very harmful'. However, the overall opinion of the efficacy of these interventions was positive (Table 5-9).

Table 5-9 Perceived efficacy of physiotherapy interventions received

		Perceived efficacy (%)				
Intervention (total n=452)	n	v harm	harm	neith	ben	v ben
Home exercise programme	373	0	1	12	58	28
Exercise with physiotherapist	320	<1	<1	6	39	54
Advice/Education	293	0	<1	8	50	41
Functional Electrical Stimulation	110	0	3	21	29	47
Standing frame	78	0	3	8	53	37
Acupuncture	43	2	5	36	31	26
TENS	30	3	10	34	34	17

Abbreviations: n: number of respondents; v: very; harm: harmful; neith: neither harmful nor beneficial; ben: beneficial; TENS: transcutaneous electrical nerve stimulation

5.2.3 Desired delivery of physiotherapy

Respondents were asked about their desired delivery of physiotherapy for their MS. Just over half (52%) of participants reported that they would like more physiotherapy than they were currently receiving, 30% were happy with the amount of physiotherapy they were currently receiving and 17% did not know whether they would like more physiotherapy or not. When asked about the desired pattern of delivery, 65% reported that they would prefer to receive physiotherapy sessions regularly and 35% reported they would prefer to receive their sessions when required. Almost two thirds of responding participants (65%) reported that they would like to receive physiotherapy for their MS at least once a week and 69% reported a desired length of physiotherapy session of 30-60 minutes. The most preferred settings for receiving physiotherapy were at home (40%) or in a hospital or clinical setting (35%). A delivery of one to one was favoured by 77% of respondents (Table 5-10).

Table 5-10 Desired delivery of physiotherapy

Variable	n	Options	n	%
Wants more physiotherapy for their MS?	946	Yes	494	52
		No	287	30
		Don't know	165	17
Desired pattern of sessions	947	Regular	617	65
		Vary depending on symptom	330	35
Preferred frequency of sessions	621	Once or more a week	332	54
		Once a fortnight	185	30
		Once every 1 to 3 months	91	15
		Twice a year	11	2
		Once a year or less	2	0
Preferred length of sessions	941	<30 minutes	238	25
		30 - 60 minutes	647	69
		>60 minutes	56	6
Preferred setting	945	At home	374	40
		In a hospital or clinic	331	35
		In a community centre	69	7
		In a charity centre	94	10
		Other	77	8
Preferred number of people present	941	One to one	725	77
		2-4 people	146	16
		5 or more people	63	7
		by telephone or online	7	1

Abbreviations: n: number of respondents

5.2.4 Barriers to accessing physiotherapy

The five most commonly reported barriers to accessing physiotherapy were mobility (40%), fatigue (39%), continence issues (21%), transport (21%), and needing someone to go with them to the appointment (21%). While 23% of respondents reported that they did not have any barriers to receiving physiotherapy. From the list of barriers the participants had selected, they were then asked to select which three were the most problematic for them. These were called the 'most problematic', 'second most problematic' and 'third most problematic' barriers.

The top three 'most problematic' barriers reported were mobility (13%), fatigue (20%), and transport problems (9%). The top three 'second most problematic' barriers were mobility (17%), fatigue (15%), transport problems (7%) and pain (7%). The top three 'third most problematic barriers' were fatigue (16%), mobility (14%), and continence issues (10%) (Table 5-11).

Table 5-11 Most commonly reported and most problematic barriers to accessing physiotherapy

Barrier to accessing physiotherapy	Most common		Most problematic barriers: First		Second		Third	
	n	%	n	%	n	%	n	%
Mobility	372	40	78	13	102	17	73	14
Fatigue	365	39	122	20	91	15	84	16
Continence issues	197	21	38	6	38	6	51	10
Transport problems	197	21	53	9	39	7	29	6
Needing someone to go with them	194	21	41	7	32	5	47	9
Distance to travel	169	18	33	5	35	6	31	6
Fear of falling	157	17	15	2	38	6	29	6
Pain	156	17	35	6	39	7	23	4
Cost	139	15	5	1	29	5	28	5
Lack of suitable parking	122	13	13	2	28	5	25	5
Issues being referred to physiotherapy	110	12	46	7	19	3	10	2
Other	96	10	26	4	13	2	11	2
Difficulty with wheelchair transfers	94	10	15	2	26	4	16	3
Physiotherapy not available	90	10	46	7	19	3	20	4
Work commitments	64	7	25	4	14	2	14	3
Lack of time	55	6	11	2	21	4	13	2
Depression	50	5	2	<1	4	1	7	1
Family commitments	44	5	3	<1	1	<1	6	1
Anxiety/panic attacks	26	3	4	1	5	1	3	1
Physiotherapy not beneficial	7	1	2	<1	0	0	1	<1
Personal issues with physiotherapist	4	<1	1	<1	0	0	1	<1
No barriers to receiving physiotherapy	215	23	-	-	-	-	-	-

Abbreviations: n: number of responses
Percentages calculated from total number of respondents to question as a whole (n=938), participants were able to choose more than one answer.

5.2.5 Complementary and Alternative Therapies

When asked regarding use and previous use of CAT, 42% (n=506) of respondents reported that they had used CAT in the prior three months for their MS (Table 5-12). The most commonly used CAT were massage (41%), Reflexology (29%) and relaxation or meditation (24%) (Table 5-12). The total number of respondents who said that they had not used a CAT was 727, however, 24 of those also reported using a CAT that was listed. They were subsequently subtracted from

the total of those who did not use CAT, thus the total number of people who did not use CAT was 703 (58%). Respondents also reported four types of exercise as a CAT: yoga (6%), pilates (6%), exercise in general (3%) and tai chi (2%).

Table 5-12 Complementary and alternative therapies used in the prior three months

Complementary and alternative therapy (total n=506)	n	%
Massage	207	41
Reflexology	146	29
Relaxation or meditation	123	24
Hyperbaric oxygen therapy	85	17
Acupuncture or acupressure	72	14
Osteopathy or chiropractic	58	11
Homeopathy or herbal medicine	40	8
Reiki	33	7
Aromatherapy	32	6
Yoga	32	6
Pilates	32	6
Dietary supplements	29	2
Exercise	14	3
Magnet field therapy	9	2
Tai chi	8	2
The Alexander technique	7	1
Bowen technique	7	1
Low dose Naltrexone	6	1
Craniosacral therapy	3	<1
Diet management	3	<1
Vibration machine	2	<1
Action potential stimulation	1	<1
Bee venom	1	<1
“Circulation booster”	1	<1
“muscle activation therapy”	1	<1
Self-Controlled Neuro-Adaptive Regulator device	1	<1
Ultrasound on legs	1	<1

Abbreviations: n: number of respondents

5.3 Association between access to a specialist and demographics, quality of life, impact of disease, use of disease modifying therapies and receiving a review

After Bonferroni adjustment, age was the only continuous variable which was different between those with and without access to an MS Specialist (p=0.001). Those who did not have access to an MS Specialist were significantly older than those who reported access (p=0.001) (Table 5-13). In addition, receiving an annual review was associated with access to an MS Specialist (p<0.001) (Table 5-14).

Table 5-13 Association between access to specialist and age, time since diagnosis, quality of life and impact of Multiple Sclerosis

	Access to Specialist	n	median	Mean Rank	*p*
Age	yes	1184	59	616.85	0.001*
	no	64	63	765.95	-
TSD	yes	1146	15	598.12	0.011
	no	61	19	714.42	-
EQ-5D-3L index	yes	1154	0.566	611.2	0.245
	no	62	0.503	558.23	-
MSIS-29 -phys	yes	1180	56	621.19	0.581
	no	64	58	646.65	-
MSIS-29 -psych	yes	1167	19	615	0.832
	no	63	18	624.73	-

Abbreviations: TSD: time since diagnosis; MSIS-29: multiple sclerosis impact scale; phys: physical sub-scale; psych: psychological sub-scale; n: number of respondents
*Statistically significant after Bonferroni adjustment (0.05/5=0.01)

Table 5-14 Difference between those with and without access to a specialist in demographics and use of disease modifying treatments

		Access to MS specialist		
	n	Yes	No	*p*
PPMS	1248	437	27	0.473
SPMS		747	37	
Past DMTs use	1227	288	11	0.371
No past DMTs use		880	48	
Current DMTs use	438	87	1	0.175
No current DMTs use		332	18	
Urban dwelling	1201	787	43	1.000
Rural dwelling		352	19	
Annual review	1233	894	15	<0.001*
No annual review		245	42	
Don't know		35	2	

Abbreviations: PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; DMTs: disease modifying therapies; n: number of respondents; MS: multiple sclerosis.
*Statistically significant result with Bonferroni adjustment (0.05/6=0.008)

5.3.1 Association between single or multiple service use and quality of life, impact of disease and use of disease modifying therapies

There were statistically significant differences, after Bonferroni adjustment, in EQ-5D-3L indexes and MSIS-29 physical and psychological sub-scales between those who recently received a single service or multiple services for their MS. Compared to respondents who had recently used a single service for their MS, those who used multiple services had a lower EQ-5D-3L index, higher physical and psychological MSIS-29 sub-scale scores indicating a poorer quality of life and higher impact of disease (all $p<0.001$) (Table 5-15).

Table 5-15 Differences between those using single and multiple services in EQ-5D-3L index and MSIS-29 physical and psychological sub-scale scores

	Single or multiple service use	n	median	Mean Rank	p
EQ-5D-3L index	single	469	0.566	563.99	<0.001*
	multiple	548	0.503	461.94	
MSIS-29 - phys	single	478	55	476.3	<0.001*
	multiple	563	59	558.95	
MSIS-29 - psych	single	473	18	462.13	<0.001*
	multiple	555	20	559.13	

*Statistically significant after Bonferroni adjustment (0.05/3= 0.017).
Abbreviations: MSIS-29: multiple sclerosis impact scale; phys: physical sub-scale; psych: psychological sub-scale; n: number of respondents

5.3.2 Association between past and present use of disease modifying therapies and quality of life and impact of disease

After Bonferroni adjustment, respondents who were currently taking DMTs had a higher EQ-5D-3L index indicating a better quality of life than those who were not taking DMTs (p=0.016) (Table 5-16). There were however, no differences in psychological or physical sub-scale scores of the MSIS-29 indicating no difference in disease impact between those who were and were not currently taking DMTs.

Table 5-16 Difference between those currently taking and not taking disease modifying therapies in EQ-5D-3L index and MSIS-29 sub-scale scores

	Current DMTs use	n	median	Mean Rank	*p*
EQ-5D-3L index	Yes	87	0.566	245.75	0.016*
	No	346	0.503	209.77	-
MSIS-29 -phys	Yes	87	57	199.17	0.05
	No	359	59	229.4	-
MSIS-29 -psych	Yes	85	20	220.88	0.96
	No	357	20	221.65	-

Abbreviations: MSIS-29: multiple sclerosis impact scale; phys: physical sub-scale; psych: psychological sub-scale; DMTs: disease modifying therapies; n: number of respondents.
*Statistically significant with Bonferroni adjustment (0.05/3=0.017)

The EQ-5D-3L index and the MSIS-29 physical and psychological sub-scales were also compared between respondents who had previously taken DMTs and those who had never taken DMTs. Following Bonferroni adjustment, a lower EQ-5D-3L index (p<0.001) and higher psychological (p=0.006) and physical sub-scale (p<0.001) scores were observed in those who had previously taken DMTs indicating a poorer quality of life and higher impact of MS compared to those who had not previously taken DMTs (Table 5-17).

Table 5-17 Difference between those who had previously taken and not taken disease modifying therapies in EQ-5D-3L index and MSIS-29 sub-scale scores

	Past DMTs use	n	median	mean rank	*p*
EQ-5D-3L index	yes	296	0.503	531.99	<0.001*
	no	912	0.566	628.03	-
MSIS-29 -phys	yes	302	59	698.49	<0.001*
	no	935	56	593.33	-
MSIS-29 -psych	yes	299	20	661.09	0.006*
	no	925	19	596.79	-

Abbreviations: MSIS-29: multiple sclerosis impact scale; phys: physical sub-scale; psych: psychological sub-scale; DMTs: disease modifying therapies; n: number of respondents
* Statistically significant with Bonferroni adjustment (0.05/3=0.017)

5.3.3 Association between access and use of physiotherapy and quality of life, impact of disease and demographics

Participants who were receiving physiotherapy were younger than those who were not receiving physiotherapy (p<0.001) and had a shorter TSD (p=0.009) (after Bonferroni adjustment) (Table 5-18). There were no differences in EQ-5D-3L index or MSIS-29 scores between those who did and did not have access to physiotherapy and those who were and were not receiving physiotherapy for their MS (Table 5-18). Urban or rural dwelling, gender, country of residence or MS type were not factors in either having access to or receiving physiotherapy (Table 5-19).

Table 5-18 Comparison between those with access to physiotherapy and those receiving physiotherapy in continuous demographic and clinical variables

		Access to physiotherapy				Receiving physiotherapy			
				Mean				Mean	
Variable		n	Med	rank	*p*	n	Med	rank	*p*
Age	Y	1118	59	629.93	<0.001*	704	59	635.07	<0.001*
(years)	N	173	61	749.84	-	166	61	648.23	-
TSD	Y	1082	14.5	615.54	0.034	680	14.0	631.12	0.009*
(years)	N	165	17.0	679.45	-	158	17.0	617.64	-
EQ-5D-	Y	1089	0.57	638.26	0.048	401	0.57	631.19	0.778
3L index	N	167	0.50	677.21	-	852	0.57	625.03	-
MSIS-29	Y	1113	56	638.26	0.199	411	57	644.72	0.83
phys	N	173	58	677.21		871	57	639.98	-
MSIS-29	Y	1102	19	633.34	0.435	403	19	599.23	0.019
psych	N	170	20	656.96	-	865	20	650.93	-

Abbreviations: TSD: time since diagnosis; MSIS-29: multiple sclerosis impact scale; phys: physical sub-scale; psych: psychological sub-scale; Y: yes; N: no; n: number of respondents; Med: median
*Statistically significant after Bonferroni adjustment (0.05/5=0.01).

Table 5-19 Comparison between those with access to physiotherapy and those receiving physiotherapy in categorical demographic variables

Variable		Access to physiotherapy			Receiving physiotherapy		
		Yes	No	*p*	Yes	No	*p*
Urban/ rural dwelling	Urban	746	110	0.418	273	581	0.861
	Rural	330	57	-	125	260	-
Gender	Female	703	115	0.361	259	557	0.666
	Male	415	58	-	155	316	-
Country of residence	England	888	139	0.557	328	695	0.803
	Scotland	113	16	-	44	85	-
	Wales	88	13	-	31	70	-
	Northern Ireland	16	5	-	5	16	-
MS type	PPMS	417	67	0.718	156	326	0.907
	SPMS	701	106	-	258	547	-

Abbreviations: MS; multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis

5.3.4 Variation in expected waiting time

Expected waiting time for a physiotherapy appointment varied depending on the provider. Most notable was that 27% of participants who received their physiotherapy from non-NHS sources expected to receive an appointment in a week or less, compared to just 2% of participants who received their physiotherapy solely from the NHS. Thirty-nine percent of those who received their physiotherapy from the NHS expected to receive their physiotherapy appointment in 4 weeks or less compared to 88% of those who received their physiotherapy from non-NHS sources (Table 5-20).

Table 5-20 Expected waiting times by source of physiotherapy

Provider of physiotherapy	n	Expected waiting time for appointment (weeks)					
		<1	1 - 2	2- 4	4- 6	6 – 12	>12
NHS	133	2%	22%	15%	28%	23%	10%
Non-NHS	26	27%	39%	23%	0%	12%	0%
Both	27	7%	11%	33%	11%	19%	19%

Abbreviations: NHS: National Health Service; n: number of responses

5.3.5 Perceived efficacy of physiotherapy

Due to the small amount of participants who regarded physiotherapy as 'harmful' or 'very harmful' to them, it was not possible to conduct statistical analysis across the levels of perceived efficacy. However, descriptively, more participants who were receiving physiotherapy thought that it was 'very beneficial' than those who were not receiving it. In addition, more participants who were not receiving physiotherapy thought that physiotherapy was 'neither harmful nor beneficial' for them than those who were receiving physiotherapy (Figure 5-3). Although physiotherapy was well thought of there was no difference in perceived efficacy of physiotherapy between the participants who thought they needed more physiotherapy for their MS, those who did not and those who did not know (Table 5-21).

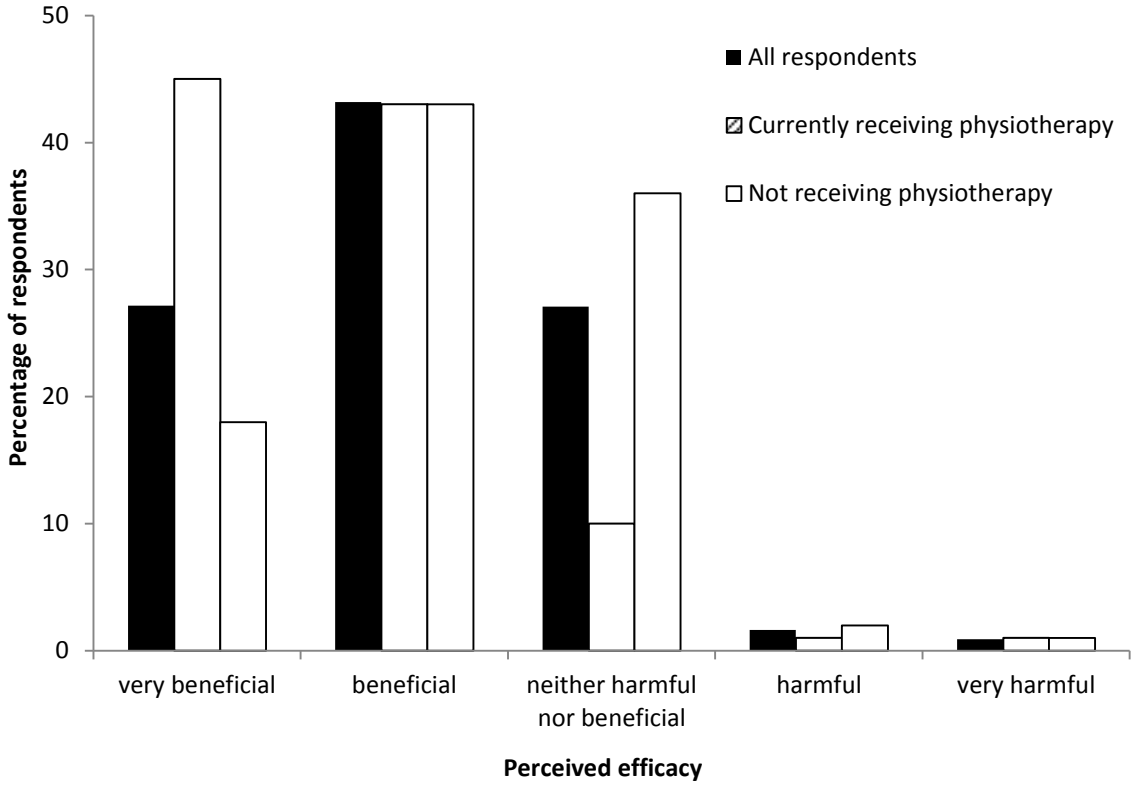

Figure 5-3 Perceived efficacy of physiotherapy of whole cohort, those currently receiving physiotherapy and those not currently receiving physiotherapy

Table 5-21 Perceived efficacy in those with access to, receiving, and wanting more physiotherapy, gender, country of residence and urban/rural dwelling

			Perceived efficacy				
			v harm	harm	neith	ben	v ben
Variable		n	%	%	%	%	%
Access to physiotherapy	Yes	640	1	3	38	44	15
	No	154	<1	1	27	40	31
Receiving physiotherapy	Yes	408	<1	<1	10	43	45
	No	795	1	2	36	43	18
Wanting more physiotherapy	Yes	462	<1	<1	3	59	37
	No	268	<1	<1	5	53	41
	Don't know	150	0	0	9	68	23
Gender	Female	766	1	2	26	40	30
	Male	442	1	2	29	48	21
Country of residence	Scotland	122	2	0	29	42	27
	England	961	1	2	27	43	27
	Wales	96	1	0	26	50	23
	Northern Ireland	20	0	5	15	40	40
Urban/Rural dwelling	Urban	800	1	2	29	44	25
	rural	366	1	2	25	43	30

Abbreviations: n: number of respondents; v: very; harm: harmful; neith: neither harmful nor beneficial; ben: beneficial

Analysis revealed statistically significant differences in the MSIS-29 physical and psychological sub-scales across the levels of perceived efficacy (Table 5-22). However, due to the small number of participants who felt that physiotherapy would be harmful or very harmful to them post-hoc analysis was not possible. There were no differences, after Bonferroni adjustment, in the MSIS-29 physical and psychological sub-scales between those who thought that physiotherapy was 'very beneficial', 'beneficial', or 'neither harmful nor beneficial' to them (p=0.025 and p=0.185 respectfully) (Table 5-23).

Table 5-22 Differences in EQ-5D-3L index, MSIS-29 sub-scales, age and TSD across all levels of perceived efficacy

Perceived efficacy		EQ-5D-3L index	MSIS-29 phys	MSIS-29 psych	Age	TSD
		n=1179	n=1203	n=1190	n=1208	n=1170
Very harmful	%	<1	<1	<1	<1	<1
	Median	0.357	65	20	58	16
	Mean Rank	492.23	779.73	627.91	555.05	580.55
Harmful	%	2	2	2	2	2
	Median	0.272	62	25	54	14
	Mean Rank	359.05	718.65	856.73	426.65	566.88
Neither harmful nor beneficial	%	27	27	27	27	27
	Median	0.503	58	20	60	15
	Mean Rank	572.25	635.03	620.33	628.48	571.8
Beneficial	%	43	43	43	43	44
	Median	0.566	56	19	59	15
	Mean Rank	605.33	571.66	580.15	613.02	585.49
Very beneficial	%	27	27	27	27	27
	Median	0.566	56	19	58	15
	Mean Rank	601.5	601.07	577.49	579.28	600.53
	P	0.014	0.013	0.004*	0.061	0.877

Abbreviations: n: number; MSIS-29: multiple sclerosis impact scale; phys: physical sub-scale; psych: psychological sub-scale; TSD: time since diagnosis
*Statistically significant with Bonferroni adjustment (0.05/5=0.01)

Table 5-23 Differences in EQ-5D-3L index, MSIS-29 sub-scale scores, age and time since diagnosis by indifferent and positive perceived efficacy

Perceived efficacy		EQ-5D-3L index	MSIS-29 phys	MSIS-29 psych	Age	TSD
Neither harm nor beneficial	%	27	27	27	27	27
	Median	0.503	58	20	60	15
	Mean Rank	572.25	635.03	620.33	628.48	571.8
Beneficial	%	43	43	43	43	44
	Median	0.566	56	19	59	15
	Mean Rank	605.33	571.66	580.15	613.02	585.49
Very beneficial	%	27	27	27	27	27
	Median	0.566	56	19	58	15
	Mean Rank	601.5	601.07	577.49	579.28	600.53
	*p**	0.36	0.025	0.185	0.178	0.567

Abbreviations: med: median; MSIS-29: multiple sclerosis impact scale; phys: physical sub-scale; psych: psychological sub-scale; TSD; time since diagnosis
*Statistical significance after Bonferroni adjustment 0.05/5=0.01.

5.3.6 Association between use of complementary and alternative therapies and quality of life, impact of disease, demographics and receiving a regular review

There were no statistically significant differences in TSD, EQ-5D-3L and MSIS-29 physical and psychological sub-scale scores between those who had and had not used CAT for their MS in the prior three months (Table 5-24). In addition, there was no association between use of CAT and country of residence, urban or rural dwelling, MS type or being in receipt of a regular review or not (Table 5-25). However, more females had recently used CAT than males (p=0.006) (Table 5-25).

Table 5-24 Differences between those who had and had not recently used complementary and alternative therapies in EQ-5D-3L index, MSIS-29 sub-scale scores, age and time since diagnosis

	Used CAT	n	median	Mean Rank	p
Age	yes	506	60	600.13	0.68
	no	703	59	608.51	-
TSD	yes	494	14	578.64	0.471
	no	679	15	593.08	-
EQ-5D-3L index	yes	491	0.566	599.67	0.408
	no	688	0.566	583.1	-
MSIS-29 -phys	yes	503	56	580.78	0.061
	no	702	57	618.92	-
MSIS-29 -psych	yes	494	19	599.72	0.818
	no	699	19	595.08	-

Abbreviations: TSD: time since diagnosis; MSIS-29: multiple sclerosis impact scale; phys: physical sub-scale; psych: psychological sub-scale; CAT: complementary and alternative therapies; n: number of respondents

Table 5-25 Differences between those who had and had not recently used complementary and alternative therapies in demographics and receipt of a regular review

		Used CAT	Not used CAT	*p*
Gender	Female	344	424	0.006*
	Male	162	279	-
Country	Scotland	51	73	0.638
	England	404	551	-
	Wales	35	63	-
	Northern Ireland	9	11	-
MS Type	PPMS	180	272	0.269
	SPMS	326	431	-
Urban/Rural dwelling	Urban	319	485	0.06
	rural	164	196	-
Receives regular review	yes	372	515	0.843
	no	110	162	-
	don't know	17	21	-

Abbreviations: MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; CAT: complementary and alternative therapies
*Statistically significant after Bonferroni adjustment (0.05/5=0.01)

5.4 Summary

In summary, the results of this survey indicate that access to MS Specialists was high at 95%, but that access to a regular review was lower at 74%, with 36% of respondents receiving their review less than annually. The most used clinical services for MS were an MS Specialist Doctor or Nurse (50%), General Practitioner (45%), and Physiotherapist (40%). Use of DMTs amongst the whole cohort was quite low at 5%, but previous use was higher with 24% of respondents reporting previously taking DMTs. Present use of DMTs was associated with a better quality of life and previous use was associated with a poorer quality of life and higher physical and psychological impact of MS.

Access to physiotherapy was high at 87%, of which 32% were currently receiving physiotherapy for their MS. As a discipline, physiotherapy was very well perceived with 70% having a positive view of it. The most commonly prescribed physiotherapy interventions were exercises with a physiotherapist, exercises to be completed independently and advice or education from a physiotherapist. These three most commonly prescribed interventions also had the highest level of perceived efficacy from the respondents. The most common barriers to receiving physiotherapy were mobility, fatigue, continence, transport issues and needing the assistance of another person for the appointment. Finally, 42% had recently used a CAT for their MS. The most commonly utilised CAT were massage, reflexology, and relaxation or meditation.

Chapter 6 Survey of clinical services for people with Multiple Sclerosis in the UK – Discussion

This chapter will discuss the results of the online survey. This was, at the time, the largest survey solely of people with progressive Multiple Sclerosis (MS) and the first to investigate service access and use in people with progressive MS in the United Kingdom (UK).

This chapter will discuss, the access to and use of clinical services, including Disease Modifying Therapies (DMTs), by people with progressive MS and comparisons to previous research both in and outwith the UK. Secondly, physiotherapy access, delivery, desired delivery, interventions received, perceived efficacy, the effect on quality of life and disease impact, and barriers to receiving physiotherapy and will be discussed. The results regarding the use of Complementary and Alternative Therapies (CAT) and the evidence surrounding the most common CAT used will then be discussed, and finally the limitations of the study and recommendations for future work will be presented.

6.1 Access to Multiple Sclerosis clinical services

Access to an MS Specialist was high (95% overall) with slight variation depending on geographical location in the UK (range 92-98%). This result was higher than the results of the 'My MS My Needs' study conducted by the MS Society which found that 86% of their respondents had access to an MS Specialist (MS Society, 2016c). This difference may be due to the fact that the present survey focussed on people with progressive MS and the survey carried out by the MS Society included people with all types of MS who will have different needs and possible different awareness of available services.

The result of this present study was however, in contrast to that of two older and smaller studies conducted in the UK. These two studies, which had either half of their sample size made up of progressive MS or focused on those severely disabled, found that access to services was poor (Edmonds et al., 2007, MacLurg et al., 2005). The qualitative study carried out by Edmonds et al. (2007), which

examined access to MS clinical services by people severely affected by MS (Expanded Disability Status Scale (EDSS) ≥8.0) in London, reported that a lack of ability to gain access to clinical services was the most common theme among the 32 participants. The results from this present survey indicated that access to an MS Specialist in the London area was 94%. Differences between these two results may be reflective of changes in service provision over the past decade and from differences in sample size as Edmonds et al. (2007) had a sample size of 32 and the sample size of this survey was 1,298 with 71 living in the Strategic Health Authority of London. Furthermore the mean physical impact of MS, as measured by the Multiple Sclerosis Impact Scale - 29 version 2 (MSIS-29), of respondents in this current study was 56/80 indicating a moderate level of physical impact while participants in Edmonds et al.'s (2007) study were severely disabled (EDSS≥8.0) which may have impacted upon ability to access services. Lastly, the participants in the study by Edmonds et al. (2007) cited organisational barriers to accessing services such as a not being able to gain access to a clinician when needed, rather than the service not existing. This implies that Edmonds et al. (2007), although not explicitly stated, used a different definition of access to the one used in this present study, as access was defined as the existence of a service regardless of organisational or environmental barriers (section 4.1.1).

Similarly a difference in definition of access may be the reason for differences seen in results between this survey and the research conducted by MacLurg et al. (2005). This study conducted in Northern Ireland, examined needs of 149 people with MS (56% with progressive MS), and reported that access to physiotherapy was an unmet need regardless of disability (21%). This is in contrast to the results of the present study which found that access to physiotherapy and MS specialists to be high in Northern Ireland (95%). The researchers did not, however, define the terms 'access' or 'unmet need'. Furthermore, 13% of the sample in the study by MacLurg et al. (2005) was receiving physiotherapy, which was lower than the 32% receiving physiotherapy in this present survey. Lastly, in this present survey Northern Ireland was the region which had the lowest number of respondents (n=21) limiting comparability of the two samples.

A survey conducted by Lonergan et al. (2015) in the Republic of Ireland had similar results to MacLurg et al. (2005). A sample of 325 people with MS (50%

progressive) answered a questionnaire regarding access to MS clinical services. The researchers reported that there was a lack of access to physiotherapy services, especially among those with progressive MS, and who lived in a rural area (Lonergan et al., 2015). This is in contrast with the results found in this present study, as 87% had access to physiotherapy services, with no differences in access to services between those who lived in rural or urban locations. It should be noted however, that not only does the Republic of Ireland have a different healthcare system to the UK, the rural/urban spread of the UK and the Republic of Ireland is substantially different. The Republic of Ireland has 37% of its population living in a rural setting compared to 18% in the UK (World Data Bank, 2016). This difference in population spread may indicate different strains placed upon services, and may explain why there was no difference between rural and urban service delivery in the UK but was in the Republic of Ireland.

Two separate qualitative research studies in Germany examined patient experience of MS clinical services (n=15, mean EDSS=7.0) (Galushko et al., 2014) and clinician opinion of MS clinical services (n=23) (Golla et al., 2012). Both studies reported that there was an unmet need in of access to services (Galushko et al., 2014, Golla et al., 2012) but cited the main reasons for this were long waiting times and a lack of home visits (Golla et al., 2012). These results are in contrast with the results of the present survey. Again, this difference may be due to differences in the definition of access, as the German participants cited organisational barriers affecting access to services. In addition, health service provision in Germany differs from that of the UK, with reports of a lack of multi-disciplinary care due to financial constraints incurred by out-patient care (Maurice, 2014), which was reflected in the patient and clinician feedback.

In general, in terms of access to MS services, the results of this survey were higher than previous research conducted. However, the difference in definitions of access may have led to these discrepancies, especially when other researchers were focusing on establishing the organisational and environmental barriers to gaining access and not measuring the availability of services.

6.2 Access to a clinical review

Despite the high rate of access to MS Specialists the proportion of those receiving annual reviews was lower at 74%. This suggests a 26% shortfall in provision in service, according to the current National Institute for Health and Care Excellence (NICE) guidelines, and Healthcare Improvement for Scotland clinical standards for the management of people with MS (NICE, 2014b, Healthcare Improvement Scotland, 2009) which state that all people with MS should receive an annual review. In addition to there being a shortfall in overall provision, there was also a shortfall in the frequency of reviews, with 37% of respondents reporting that their review was less often than annually. This is again in contradiction to the NICE guidelines and Health Improvement Scotland standards. The importance of a regular review may increase in the future with the potential advent of a new disease modifying therapy for people with Primary Progressive MS (PPMS) becoming available on the NHS (European Medicines Agency, 2017), as without a review suitable patients for the new disease modifying therapy could potentially be overlooked.

6.3 Use of Multiple Sclerosis clinical services

The most utilised clinical services for the respondents' MS were an MS Specialist Doctor or Nurse (50%), General Practitioner (45%), Physiotherapist (40%) and Occupational Therapist (24%). These results were in agreement with the GEMMS study conducted by Mynors et al. (2015), which found that the MS nurse was the most utilised practitioner. The UK results from a European wide study conducted by Kersten et al. (2000) (n=37), found that the most consulted clinicians were the same, but were consulted by a greater proportion of their sample: General Practitioner (95%), MS specialist (84%), Physiotherapist (62%) and Occupational Therapists (62%). The similarity of clinicians consulted but difference in rate of utilisation between the study by Kersten et al. (2000) and this present survey may indicate that the use of clinical services is similar between those with Relapsing Remitting MS (RRMS) and progressive MS but that services used by patients may have reduced over the past 17 years. However, the small sample

size representing the UK in the study by Kersten et al. (2000) may limit comparability between the two studies.

6.4 Disease modifying therapies

Five percent of this cohort were currently taking DMTs and 24% reported historic use of DMTs. This result is in contrast with the survey conducted by the MS Society which found that 56% of their cohort were taking a DMTs (MS Society, 2016c). This difference in results is to be expected, as 57% of their cohort either had RRMS or Secondary Progressive MS (SPMS) but were still experiencing relapses and were therefore appropriate for DMTs prescription (Scolding et al., 2015).

Analysis revealed that current use of DMTs was associated with a better quality of life and previous use of DMTs was associated with a worse quality of life and worse physical and psychological disease impact. This is, again, as expected as respondents who are currently taking DMTs are likely to be in the early stages of SPMS and may still be experiencing relapses, and thus, are likely to have a lower level of disability and better quality of life (Scolding et al., 2015). Respondents not taking DMTs are, by definition, no longer experiencing relapses and thus, may experience greater disability and reduced quality of life (Scolding et al., 2015). This is however, dependent on having access to DMTs which previous research has shown to vary across the United Kingdom (MS Society, 2016a, MS Society, 2016b).

6.5 Physiotherapy

6.5.1 Access

Access to physiotherapy was high (87%) and 32% reported that they were currently receiving physiotherapy for their MS. Despite the high rate of access, this indicates a lack in service provision of 13%. This percentage of respondents without access to physiotherapy was similar to a result reported in the survey by

the MS Society which found that 17% did not have access to a physiotherapist (MS Society, 2016c). The slightly higher access figures in this present study may be due to those who have progressive MS, and likely higher disability, being more aware of their services available to them.

The present survey found that 40% of the cohort received their physiotherapy from non-NHS sources, which is a slightly higher result found from the survey by the MS Society, which found that 32% of their cohort received their physiotherapy from non-NHS sources (MS Society, 2016c). The non-NHS sources used by respondents in this present survey were made up of self-funded private physiotherapy (20%), physiotherapy provided by a charity (16%), and medical insurance funded private physiotherapy (2%). If 16% of all physiotherapy care for people with progressive MS is being delivered by the third sector, this could indicate that, while these organisations are providing a valuable service to their clients, the NHS is not able to deliver the physiotherapy services that people with MS need and want. Furthermore, previous research has shown that perceptions of physiotherapy service delivery, for people with MS, were predominantly negative in the UK (Markwick et al., 2014). If, as was found in this present study, people with progressive MS have a high perceived efficacy of physiotherapy as a discipline, but a low opinion of the service delivered, they may seek out other avenues of physiotherapy delivery, for example private or charity-based physiotherapy. Further investigation is warranted to explore this further.

6.5.2 Delivery of physiotherapy and waiting times

Physiotherapy was predominantly delivered in either a clinical or hospital setting (46%), at home (25%), or in a charity centre (24%). The survey conducted by the MS Society found that 74% of MS care was in a hospital or clinical setting, only 16% was provided at home and 12% of care was provided in a charity centre (MS Society, 2016c). It should be noted however, that the MS Society survey included people with all types of MS and the questions that were asked were related to MS care in general and not only physiotherapy. Furthermore, as the cohort from the current study all had a diagnosis of progressive MS they were more likely to

have a higher impairment compared to those with RRMS (Compston and Coles, 2008). Having a higher level of impairment may lead to care being more likely to be received at home and previous research in Australia has shown that an increase in domiciliary care can lead to rationing of services and decreased volume of individual care (Adams et al., 2015). While this would still mean that they had access to these services, the quantity of services provided may be reduced and the overall needs of the patient may not be met.

Ninety percent of this cohort expected to receive a physiotherapy appointment within 12 weeks. However, NHS waiting time targets vary across the four countries of the UK. In Scotland the target waiting time for an outpatient appointment is 12 weeks (Scottish Government, 2011). In Wales and England the target waiting time for an outpatient NHS appointment is 18 weeks (NHS England, 2016). In Northern Ireland the target for receiving an outpatient appointment is more complex. In 2015 they had a target of at least 80% receiving an appointment in nine weeks with no patient waiting more than 15 weeks (Department of Health, 2015). In 2017 this was revised to 50% of patients should be seen in nine weeks and no patient should wait longer than 52 weeks for an outpatient appointment (Department of Health, 2017). Initially this would imply that the respondents in this survey expected to be seen within the waiting time targets in their respective country. However, this study measured expected waiting time and not actual waiting times. A report by JJ Consulting (2011) summarised waiting times across the UK for physiotherapy appointments and found 83% of neurology patients were seen by a neurological physiotherapist in the NHS in eight weeks or less (JJ Consulting, 2011). Unfortunately the researchers did not have data on individual conditions such as MS, and the comparison of the results between the report by JJ Consulting and this present study should therefore be treated with caution.

The positive result of the expected waiting time being less than the NHS targets is, however, nuanced as the expected waiting time of the respondent varied depending on their provider of physiotherapy. If a respondent received their physiotherapy only from non-NHS sources they were more likely to expect a shorter waiting time (27% less than a week and 39% expected in 1-2 weeks). This is substantially different from those who received their physiotherapy only from the NHS as just 2% expected to receive their appointment in less than a week

and 22% expected to be seen in 1- 2 weeks. This may explain further, why people with MS use charity based and private services.

6.5.3 Desired Delivery

Half of respondents (52%) reported that they would like more physiotherapy for their MS and the most common desired delivery of physiotherapy was: regularly, once a week, to be delivered at home, in a one to one setting with sessions lasting 30-60 minutes. This is similar to the current model of physiotherapy delivery received by respondents. The only difference was that current delivery was mainly delivered in a clinical or hospital setting. Similarly a previous survey found the majority of all MS care was delivered in a hospital or clinical setting, due to this the MS Society called for more home-based care to be delivered from the NHS (MS Society, 2016b). The results of this current survey demonstrate that the recommendation from the MS Society is aligned with the desires of this sample of people with progressive MS. However, delivery of services in this way would require increased provision of community-based care, which requires further resources to avoid rationing of services which can, as was previously stated, result in a decrease in quantity of therapy delivered, especially for those living rurally (Adams et al., 2015).

6.5.4 Interventions received

The most common physiotherapy interventions recently received for the respondent's MS, were exercises to be completed independently (83%), exercises with a physiotherapist (71%) and advice or education from a physiotherapist (65%). Less frequently prescribed physiotherapy interventions were functional electrical stimulation (24%), standing table (17%), acupuncture (10%) and Transcutaneous Electrical Nerve Stimulation (TENS) (7%). All of these interventions received, apart from acupuncture, advice and TENS, have positive evidence for their efficacy in the rehabilitation in people with progressive MS (Chapter 3). The systematic review in Chapter 3 found that there was no evidence for the use of acupuncture in people with progressive MS (Donnellan

and Shanley, 2008). In addition, there is no evidence for the use of advice and education in people with progressive MS, although a Cochrane review of ten RCTs, found that provision of information increased knowledge of the disease of MS (Kopke et al., 2014). However, the results were inconclusive of the effects that information provision had on quality of life and on decision making but did highlight that there were no negative effects (Kopke et al., 2014). While there are no trials investigating the effect of TENS in people with progressive MS there is substantial evidence that it is effective in the treatment of pain (Sawant et al., 2015) and spasticity in MS (Fernandez-Tenorio et al., 2016). Interestingly TENS was the intervention which had the greatest negative perceived efficacy from respondents. This is discussed in more detail in section 6.5.5.

The fact that almost all of the interventions received have positive evidence for their use in people with progressive MS, is a reflection of evidence-based practice that is implemented by UK physiotherapists. This is a sign of good quality care and compliance by UK physiotherapists with the Standards of Proficiency laid out by the Health and Care Professions Council (Health & Care Professions Council, 2014).

6.5.5 Perceived efficacy

Physiotherapy was generally perceived positively with 70% of respondents perceiving it to be either 'beneficial' or 'very beneficial' for their MS, and contrastingly only 3% felt that it would be harmful. Respondents were more likely to think that physiotherapy was 'very beneficial' if they were receiving physiotherapy and more likely to have an indifferent view if they were not receiving physiotherapy (Figure 5-3). These results were in contrast to the study conducted by Markwick et al. (2014), exploring opinions of clinical services for people with MS in England and Wales; which found that comments made were predominantly negative and that physiotherapy received the most negative comments out of all disciplines. Differences in results may lie in differences in methodology as respondents in the present study were asked about the effect they thought physiotherapy would have on them and Markwick et al. (2014) asked the opinion of the service delivered not the efficacy of the discipline.

Studies conducted outwith the UK, produced findings similar to the results of the current survey. The three Scandinavian studies (Holmoy et al., 2012, Normann et al., 2012, Ytterberg et al., 2008) found that the opinion of physiotherapy was predominantly positive, with results ranging from 88% to 100% positive. However, all three studies recruited participants from single neurology clinics. This will have created sample bias and may not be representative of the MS population, or service provision, of their respective countries.

The most commonly prescribed physiotherapy interventions were also the interventions that had the highest perceived efficacy from the respondents (section 5.2.2 and Chapter 3). The intervention that had the largest proportion of negative opinions was TENS, with 13% of recipients considering it as 'harmful' or 'very harmful'. This opinion is in contrast with two systematic reviews which concluded that TENS was both safe and effective in treating pain and spasticity in people with MS (Fernandez-Tenorio et al., 2016, Sawant et al., 2015). It was however, noted by Sawant et al. (2015), that MS type may affect the efficacy of TENS but neither review suggested that it was harmful. Furthermore respondents to this survey were not asked for which symptoms the interventions were prescribed, and the general opinion of TENS was still positive with 52% suggesting that it would be either 'beneficial' or 'very beneficial' for them.

6.5.6 Barriers to receiving physiotherapy

The most commonly reported barriers to receiving physiotherapy were mobility, fatigue, continence issues, transport issues and needing someone to go with them to the appointment. Respondents were then asked to select their three most problematic barriers. The outcome of which was the same barriers but also included pain. Overall, these barriers can be separated into two categories: logistic (transport problems and needing someone to go with them) and symptomatic (mobility, fatigue, continence and pain). A previous study examining barriers to exercise among people with MS found similar barriers to those found in the current survey (Asano et al., 2013). When non-disease specific barriers such as lack of time or money were excluded the most commonly

reported barriers in Asano et al.'s study were fatigue (87%), impairment (60%), needing assistance from someone else (22%) and transport issues (18%).

The logistic barriers (transport problems and needing someone to go with them) could be addressed by an increase in home-based care or provision of volunteer drivers for appointments. As already discussed, one of the recommendations from the survey conducted by the MS Society (2016b) was an increase in home-based care for people with MS; and there are some NHS health boards in Scotland which already provide volunteer drivers for patients to attend appointments (NHS Ayrshire & Arran, 2016). Additionally, steps could be taken by service providers to address the symptomatic barriers by establishing the needs of the patient from consultation and being pro-active to address them. For example, a patient who has identified that they have issues with continence or fatigue could have clearly signposted nearby toilets and adjusting timing of their appointments to a time of day when their fatigue is at its least debilitating.

6.5.7 Quality of life and disease impact

There were no differences in disease impact or quality of life scores in those who did and did not have access to an MS Specialist. As this was a cross-sectional study, it was not possible to draw causality, or lack thereof, between these variables. However, those who received more than one clinical service for their MS had a poorer quality of life (EQ-5D-3L index), and worse psychological and physical disease impact scores (MSIS-29 version 2), compared to respondents who only received one clinical service. This may be expected as those who had a poorer quality of life and a higher impact of disease would warrant more services to manage their symptoms.

Having access to a physiotherapist or being in receipt of physiotherapy was not associated with differences in quality of life or disease impact measures. Interestingly those who desired more physiotherapy than they currently received for their MS, had a poorer quality of life and higher physical and psychological impact of MS, than those who were happy with their current physiotherapy provision. This desire for more physiotherapy, when having a poorer quality of life, may arise from the high perceived efficacy of physiotherapy held by the

respondents. However, even though there is evidence to support the use of exercise, which is among the most commonly prescribed interventions in this sample, in improving quality of life in people with MS (Dalgas et al., 2010, Latimer-Cheung et al., 2013) being in receipt of physiotherapy, as a discipline, is not associated with a better quality of life (Yamout et al., 2013).

While statistically significant differences in quality of life and disease impact measures were found, the differences were small and not likely to be clinically significant. In MS, the Minimal Clinically Important Difference (MCID) of the EQ-5D-3L index ranges from 0.065-0.158 when compared to the Patient Determined Disease Steps and 0.068-0.098 when compared to the MS Walking Scale-12 (Kohn et al., 2014). The largest difference observed in the EQ-5D-3L index between any two sub-groups analysed in this present study was 0.063 between those with PPMS and SPMS, indicating that a difference in quality of life, while statistically significant, was not clinically significant.

Similarly the MCID of the physical sub-scale of the MSIS-29 version 1 is a difference of eight points (Costelloe et al., 2007b) and in the psychological sub-scale a decrease of six or more is deemed to be clinically significant (Widener and Allen, 2014). The largest difference in MSIS-29 physical sub-scale scores was between participants with PPMS and SPMS, was three points. While there is no MCID data for version 2 of the MSIS-29, this difference while statistically significant, may not be clinically significant.

6.6 Complementary and alternative therapies

In total, 38% of respondents reported that they had used a CAT for their MS in the prior three months. This result is lower than that from previous research carried out in Germany (67%), the United States of America (58%), and the Nordic countries (46-58%) (Apel et al., 2006, Skovgaard et al., 2012, Stoll et al., 2012). Conversely, CAT use in Turkey was lower, with 26% of people using a CAT for their MS (Gedizlioglu et al., 2015). The lower proportion of people using CAT in the current study compared with previous research conducted in Germany, the United States of America and the Nordic countries, may be due to the

majority of participants in other studies having RRMS with time since diagnosis between seven and nine years (Apel et al., 2006, Gedizlioglu et al., 2015) whereas the current study focussed on people with progressive MS, with a mean time since diagnosis of 16 years. It is known that people with MS are more likely to try using CAT in the early stages of their disease course (Kochs et al., 2014), however the analysis in this present study found that time since diagnosis was not a factor in the current use of CAT.

There were no differences between those who had or had not recently used CAT in terms of quality of life, disease impact scores, time since diagnosis, MS type or living in a rural or urban location. Use of CAT was however, dependent on gender, with recent CAT use higher in women. Previous research examining gender and use of CAT is heterogenic. Two previous studies found that CAT use was higher amongst women (Skovgaard et al., 2012, Stoll et al., 2012) while one study found that CAT use was not dependent on gender (Apel et al., 2006).

The most commonly used CAT in the current study were massage (41%), reflexology (29%), meditation (24%), hyperbaric oxygen therapy (17%), acupuncture (14%), chiropractic (11%), herbal medicine or homeopathy (8%) and Reiki (7%). Similarities were found between this result and that of previous research. Acupuncture was reported amongst the most commonly used CAT in the United States, Denmark, Sweden, Finland, Iceland and Norway (Skovgaard et al., 2012, Stoll et al., 2012). In the United States, like the United Kingdom, massage was the most used CAT (Stoll et al., 2012), and it was the fifth most popular in Germany (Apel et al., 2006). However there were also differences between the most commonly used CAT by this study's sample and that of samples from other countries. Hyperbaric oxygen therapy was not reported as a commonly used CAT in any of the previous research. Reflexology, the second most used CAT by this present study's sample, was only popular in Denmark and not any of the other countries previously surveyed. Lastly, CAT use in the Nordic countries was dominated by supplements (range of use 58-80%) while in this present sample just 2% had recently used a supplement for their MS.

Differences in CAT used in the present study and the findings from previous research may be because the present study focussed only on people with progressive MS in the UK, and previous research has included participants with

all types of MS. Furthermore, differences in cultural perceptions of CAT may also be responsible for differences seen from country to country (Olsen, 2009). Lastly, differences in methodology may have been responsible for differences in data collection. The Nordic and American studies, like this present study, collected data from closed question surveys while the German research used semi-structured interviews.

Exercise was cited as one of the most common CAT in all previous research. In this present study, pilates, yoga or Tai Chi were cited 86 times as a CAT used recently by the sample in this present study. There is a compelling argument that these interventions fall under the umbrella of exercise and physical activity, and thus physiotherapy (Lan et al., 2008, Smith et al., 2011, Wells et al., 2012).

6.7 Differences between Multiple Sclerosis type

When compared to the respondents who had SPMS, those who had PPMS were older, had a shorter time since diagnosis, a better quality of life and less of a psychological and physical impact of MS. Differences in quality of life and disease impact are likely explained by the shorter disease duration as time since diagnosis is a prognostic factor of impairment and quality of life (Damasceno et al., 2013). However, it should be noted, as was explained in section 6.5.7 that these differences were not clinically significant. This may explain why there were no differences in other variables between those with SPMS and PPMS such as access to specialists, access to physiotherapy, receiving physiotherapy or a regular review or the use of CAT.

6.8 Limitations

This survey was limited by its cross-sectional design, meaning that it was not possible to draw causality between any variables from results that were found.

However, as this is the first study to focus on service access and use in people with progressive MS in the UK it lays the foundations for future work.

Participation in the UK MS Register is voluntary and therefore it has the potential for sample bias to those 4,384 members who were active in their use of the register. Furthermore it also has the potential to miss those who are very severely affected by MS, as they may find completing online questionnaires more difficult. One of the other limitations of surveying people through the UK MS Register is that currently respondents self-report their diagnosis of MS and progressive MS. Thus it is possible, that some respondents did not have progressive MS or even MS at all. However, the large sample size of this study should attenuate any bias created. In addition, the long term plan of the UK MS Register is to form data links with clinical data from the NHS. This should in time eliminate this limitation entirely for future studies.

There was a lack of geographical data available for those living in Northern Ireland. This meant that comparison of rural/urban locations was not possible for this part of the UK. Furthermore, respondents from Northern Ireland made up just 2% of the cohort.

Due to the programming of the online survey some respondents did not answer all of the questions. The question which respondents most often missed was about expected waiting times for a physiotherapy appointment. This question was in the first section of the survey. Participants may have missed this question due to problems with memory recall, and not due to the length of the survey, as questions later in section three had a high number of responses (n=1,248). As just 192 participants successfully completed this question, this meant that, despite the sample size being 1,298, just these 192 completed the survey in its entirety.

Due to a programming error at the UK MS Register the clinical professions of MS Doctor and MS nurse were combined. It was therefore not possible to consider each of these professions separately and thus the results were presented together. Lastly, due to restraints from ethical approval, it was not possible to compare the demographics, quality of life and disease impact measures of those on the UK MS Register who did and did not answer the survey.

6.9 Recommendations, future work and conclusions

Despite the high levels of access to physiotherapy and MS Specialists 5% of respondents did not have access to an MS Specialist, 26% did not have access to a regular review for their MS, and 13% of people with progressive MS did not have access to a physiotherapist. These are short comings when compared to the guidelines and standards set in the UK which state that all people with MS should have access to these services (Healthcare Improvement Scotland, 2009, NICE, 2014b). Service providers should make steps towards addressing these gaps. Also, some barriers were highlighted in accessing physiotherapy, some of which were modifiable and could be addressed.

Further research should be conducted, to investigate the reasons for people with progressive MS seeking out physiotherapy services from non-NHS sources, and if the reasons are related to opinions of NHS services. Lastly a second survey may be warranted with the same respondents at a later date to examine changes in impairment and quality of life over time, potentially draw deeper understanding of the cohort as their disease progresses, and to also monitor potential changes in progression.

In conclusion this study was the first to examine access and use of services by people with progressive MS in the UK. As such it had the largest sample solely made up of people with progressive MS to be surveyed to date. The outcome of the survey showed that access to physiotherapy, and MS Specialists was high. Whilst this was promising, this does indicate that 5% did not have access. Furthermore, a greater lacking was found in the provision and delivery of regular reviews, as such, service providers should aim to address this gap.

Chapter 7 High intensity interval training in people with progressive Multiple Sclerosis

This chapter will present a brief overview of exercise and aerobic fitness in Multiple Sclerosis (MS) before discussing the effect exercise has on Brain Derived Neurotrophic Factor (BDNF), blood lipids, mental processing speed and fatigue. High Intensity Interval Training (HIIT) will then be defined before presenting a systematic review of the literature for using HIIT in people with MS, which will highlight gaps in the current literature. This systematic review has been submitted for publication in Multiple Sclerosis and Related Disorders.

7.1 Exercise and aerobic fitness in Multiple Sclerosis

Exercise is a safe and feasible intervention for people with MS, is recommended for increasing cardiovascular fitness and muscular strength (Latimer-Cheung et al., 2013), and evidence suggests that it may have a small effect on fatigue (Heine et al., 2015) and quality of life (Motl and Gosney, 2008). Cardiovascular fitness in people with MS is lower compared to healthy individuals (Langeskov-Christensen et al., 2015) and is inversely correlated with disease severity and impairment, with fitness and conditioning decreasing as disability and fatigue rises (Heine et al., 2014, Heine et al., 2016, Kuspinar et al., 2010, Motl and Fernhall, 2012, Marrie and Horwitz, 2010, Valet et al., 2016). Reviews of trials evaluating the effects of exercise in people with MS have indicated that exercise training is beneficial for reversing deconditioning, and thus increasing cardiovascular fitness (Dalgas et al., 2008, Rietberg et al., 2005).

7.2 Brain Derived Neurotrophic Factor

Brain derived neurotrophic factor is a 252 amino acid protein, coded by the BDNF gene, which stimulates growth of new neurons, promotes synaptic conductivity and supports the survival of existing neurons in both the central and peripheral nervous systems (Johnston, 2009). It has been linked to

neuroplasticity and, of all the neurotrophins, is the most responsive to exercise (Knaepen et al., 2010).

Exercise and physical activity can increase the expression of the BDNF gene and upregulate BDNF in some brain areas, most notably the hippocampus, which is responsible for learning and memory processes (Vaynman and Gomez-Pinilla, 2005). In rat models, larger BDNF responses are seen with higher levels of exercise, and dips in BDNF levels with a decrease in exercise (Neeper et al., 1995).

Resting serum concentrations of BDNF can vary in healthy (non-trained) subjects with a review of human studies reporting concentrations ranging from 1.5 to 30.9 ng/ml (Knaepen et al., 2010). Serum BDNF concentrations are altered by a number of cardiovascular disease risk factors such as Body Mass Index (BMI) and glucose tolerance (Suwa et al., 2006), neurological diseases such as Parkinson's and Alzheimer's disease (Ventriglia et al., 2013), depression and anxiety (Rabie et al., 2014), sex, fitness and lifestyle factors such as binge drinking (Bus et al., 2011).

Neurotrophins are either released continuously when they are synthesised to maintain a constant concentration or stored in secretory granules and released in response to extracellular stimuli (Farhadi et al., 2000). Brain derived neurotrophic factor is produced and stored in this latter way and exercise can increase the level of the transcriptional regulator cAMP response element binding protein, which decreases the impact of downstream effectors on BDNF, resulting in increased upregulation of BDNF (Vaynman et al., 2003). Once BDNF has been produced in the brain, it is able to cross the blood brain barrier, hence its presence in peripheral circulation (Poduslo and Curran, 1996, Pan et al., 1998). In healthy individuals BDNF serum concentrations increase both during and after an acute bout of exercise (Rasmussen et al., 2009, Ferris et al., 2007, Seifert et al., 2010). Along with increased levels of BDNF there is also an increased absorption rate by tissues and generally, BDNF serum concentrations return to baseline levels after 10-60 minutes (Knaepen et al., 2010).

A recent meta-analysis of 29 studies investigating the response of BDNF levels to training in healthy adults found that resting concentrations of BDNF in both

plasma and serum were modestly higher after aerobic training programmes but not after resistance training programmes (Dinoff et al., 2016). Another meta-analysis of 29 studies reported an increase in BDNF in response to a single bout in healthy individuals and a modest increase in resting concentrations after training but also, that training increased the BDNF response to a single bout of exercise (Szuhany et al., 2015). The authors did note, however, that even though there were increased levels of BDNF in circulation this did not necessarily mean that cerebral levels were also raised (Szuhany et al., 2015). This is an important point when examining the results of exercise studies as BDNF is predominantly measured in peripheral serum.

7.3 Brain Derived Neurotrophic Factor in people with Multiple Sclerosis

To date, there have been seven studies that have investigated the effect of aerobic exercise on BDNF concentration levels in people with MS (Bansi et al., 2013, Briken et al., 2016, Castellano and White, 2008, Gold et al., 2003, Schulz et al., 2004, Wens et al., 2016, Zimmer et al., 2017). Four studies investigated the effect of both a single bout of exercise and the effect of training on resting BDNF levels (Bansi et al., 2013, Briken et al., 2016, Castellano and White, 2008, Schulz et al., 2004), two studies investigated just the effect of training on resting levels (Wens et al., 2016, Zimmer et al., 2017) and one study investigated just the effect of a single bout of exercise (Gold et al., 2003). Reported mean resting levels of BDNF ranged from 4.435 ng/ml (Schulz et al., 2004) to 24.663 ng/ml (Zimmer et al., 2017) (Table 7-1). However, previous research has shown that the brand of Enzyme-Linked Immunosorbent Assay (ELISA) kit used to measure BDNF concentrations can have an effect on the result (Polacchini et al., 2015). Indeed the three lowest concentrations reported were within 1 ng/ml of each other and all used the same ELISA kit from Promega-Emax™. All other measurements obtained using different brands of ELISA kit were more than double the concentrations of those made with a Promega-Emax™ kit (Table 7-1). However, other factors such as lifestyle and BMI may have also affected BDNF levels (Suwa et al., 2006) indicating that differences in baseline measurements could be multi-factorial.

Table 7-1 Evidence table for studies investigating response of brain derived neurotrophic factor to exercise

Authors, Year	MS type, EDSS	Design	Intervention	Time points, ELISA kit	Baseline BDNF (ng/ml)	Response to single bout	Response to training
Bansi et al. 2012	N=60 MS type NR EDSS 1-6.5 Mean 4.7	RCT Aqua cycling Vs Land cycling	Aqua: 3 wk, 5 x wk, 30 min 60% VO_2max cycling Land: a/a but on land	Resting, 0 min post test 0 wk, 4 wk Millipore	Aqua; 14.522 Land: 19.410	O wk: no changes in either group 3 wk: Aqua: increase after stress test +4.519 ng/ml (p=0.002)	Increase in aqua group resting +3.387 (p=0.046)
Briken et al. 2016	PP: 11 SP: 31 EDSS: 4.9 (0.8)	RCT MS ex vs MS no ex	Ex: 9 wk, 2-3 x wk aerobic interval training (intensity not given) C: wait list	Resting, 0 min post-test, 30 min post-test 0 wk, 9 wk Promega	5.203 (SD 1.511)	0 and 9 wk: All participants increased immediately (p<0.001), 30 min dropped below baseline (p<0.05) No diff between groups	No change in either group (p=0.27)
Castellano and White 2008	N=22 RR: 11, HC: 11	CT	8 wk , cycling, 3 x week, 30 min, 60% VO_2 peak	BDNF resting, 30 min, 2 hour post, and 3 hour post	MS: ~10.000 (SD 10.000)	All participants: Decrease 2hr and 3 hr after ex at 0,4, and 8 wks (p<0.001)	WG MS group increase at 4 wks (p=0.04) No change in controls

	Mean EDSS 3.4			stress test. 0 wk, 4wk, 8 wk R&D systems	HC: ~20.000 (SD 15.000) (*p*=0.026)	No difference in AUC response between wk 0,and wk4 (*p*=0.2) or wk 8 (*p*=0.3)	at 4 wks or 8 wks. No diff in resting concentration BG at 8 week (*p*=0.07) (i.e. increase in MS group)
Gold et al. 2003	N=25 with MS N=20 matched HC MS: RR: 20, SP: 4, PP: 1 Mean EDSS 2.3	CT MS vs HC	30 min 60% of VO_2max	Resting 0 min post test 30 min post test Promega	MS: 4.435 (SD 0.533) HC: 4.717 (0.492) *(p*=0.1)	0 min: increase ~1.500 ng/ml 30 min: returned close to baseline No diff between groups (*p*=0.03)	n/a
Schulz et al. 2004	N=26 RR: 19 SP: 5 PP: 2 Mean EDSS 2.3	RCT MS ex vs MS no ex	Ex: 8 wk, 2 x wk, 30 min 75% peak power C: nil BDNF measured after 30 min, 60% VO_2max stress test: pre, immediate post, 30 min post	Resting, AUC from resting, 0 min, 30 min post test Promega	EX: 4.353 (SD 3217) C: 5.081 (SD 2312) (*p*=0.24)	AUC Not diff between groups. (*p*=0.18) Resting to 30 min post concentrations not reported	No diff BG resting (*p*=0.17)

Wens et al. 2016	N=41 MS: 22 HC: 19 (comparison at baseline) RR: 22 Mean EDSS: 2.6	RCT MS ex vs MS no ex (both compared to HC at baseline)	Ex: 24 wk, 5 x 2wk Aer+Res Aer: start 1 x 6min progressing to 3x 10 min 12-14 Borg RPE Res: leg press, curl, extension, vertical traction, arm curl, chest press all 1 x 10 reps, prog to 4x 15 reps, Borg RPE: 12-14 . C: no training.	Resting 0 wk, 24 wk Meso Scale Discovery	MS: 11.978 (SD 0.785) HC: 15.200 (1.124) (*P*=0.02)	n/a	24 wk: BG diff (*p*=0.04) but change only sig WG in C WG: C: -10.5% (SD 4.1) (*p*=0.02) Ex: +13.9% (SD 8.8) (*p*=0.1)
Zimmer et al. 2017	N= 60 MS:RR: 33, SP: 27 EDSS range 1.0-6.5 Mean 4.37	RCT HIIT vs CONT	HIIT vs CONT 3 wks, HIIT 3 x wk, CONT: 5 x week HIIT: 20 min, 5x 3 min intervals at 85-90% of HRMax, with 1.5 min working rest at 50-60% HRMax CONT: min 70% HRMax	Resting 0 wk, 3 wk R&D systems	HIIT: 20.965 (SD 10.606) CONT: 19.286 (SD 11.234)	n/a	No change seen in HIIT or CONT groups Final HIIT concentration 24.663 (SD 13.019)

Abbreviations: EDSS: expanded disability status scale; n: number of participants; NR: not reported: MS: multiple sclerosis; PP: primary progressive; SP: secondary progressive; RR: relapsing remitting; HC: healthy controls; RCT: randomised controlled trial; vs: versus; ex: exercise; CT: controlled trial; HIIT: high intensity interval training; CONT: continuous moderate intensity training; min: minute; VO2max: maximal oxygen uptake; a/a: as above; wk: week; hr: hour; C: control group; BDNF: brain derived neurotrophic factor; aer: aerobic training; Res: resistance training; Borg RPE: borg scale of perceived exertion; AUC: area under curve; WG: within group; BG: between group

7.3.1 Effect of an acute bout of exercise on levels of Brain Derived Neurotrophic Factor in people with Multiple Sclerosis

An increase in BDNF concentrations following an acute bout of exercise was found in four of the five studies (Bansi et al., 2013, Briken et al., 2016, Gold et al., 2003, Schulz et al., 2004) (Table 7-1). Conversely, Castellano and White (2008) reported a decrease in serum BDNF concentrations following their exercise stress test. While their exercise test of 30 minutes at 60% of VO_2max, was similar to that of both Bansi et al. (2013) and Gold et al. (2003), they differed in the time points that samples were collected. Castellano and White (2008) collected samples 30 minutes after the stress test while all other studies collected samples immediately on completion of the test. However, Briken et al. (2016) reported an increase in BDNF immediately following the exercise stress test which then dropped to below baseline 30 minutes later, and Gold et al. (2003) reported that their samples had returned to close to baseline 30 minutes after the stress test. This may explain the heterogeneity in the results, but neither of these two studies took measurements later than 30 minutes. It has been suggested that the 30 minute gap between finishing the exercise test and taking samples by Castellano and White (2008) is the reason that an increase was not seen (Knaepen et al., 2010). Of note the concentrations of BDNF from healthy controls in the study also decreased and was not statistically different from the MS participants (Castellano and White, 2008). Indeed the two studies which used healthy controls (Castellano and White, 2008, Gold et al., 2003), did not find any difference in the changes in BDNF levels between the MS participants and healthy controls. This indicates that the response of BDNF concentrations to an acute bout of exercise may be similar to that of healthy individuals.

7.3.2 Effect of aerobic training on levels of Brain Derived Neurotrophic Factor in people with Multiple Sclerosis

While the evidence for a positive response to BDNF levels to a single bout of exercise is strong, the evidence for the effect of training on resting BDNF concentrations is inconclusive in people with MS. From the six studies that

investigated the effect of training on resting serum levels of BDNF, three found an increase after their intervention (Bansi et al., 2013, Castellano and White, 2008, Wens et al., 2016) and three did not find any changes (Briken et al., 2016, Schulz et al., 2004, Zimmer et al., 2017) (Table 7-1).

Schulz et al. (2004) compared resting BDNF concentrations of a training group and a control group of people mildly affected by MS (mean EDSS 2.3), and who predominantly had RRMS. The training group received eight weeks of twice weekly training sessions of 30 minutes of cycling at 75% of peak power. The control group received no training. The researchers found no difference in resting BDNF concentrations between the groups at baseline or after the exercise intervention. Another study by the same research group, Briken et al. (2016), also found no change in resting BDNF concentrations of their intervention or control group when they compared 9 weeks of aerobic training (intensity not reported), two to three times per week to no training. Briken et al. (2016) were the only research group to recruit people solely with progressive MS and a higher disability level (mean EDSS 4.9). The third study not to find a change in BDNF levels after training was conducted by Zimmer et al. (2017). These researchers compared 3 weeks of thrice weekly HIIT at 85-90% HRMax to continuous moderate intensity training 5 times per week at 50-60% of HRMax (Zimmer et al., 2017). The cohort comprised participants both with RRMS and SPMS who were moderately disabled (mean EDSS of 4.4) (Table 7-1).

Wens et al. (2016) conducted a RCT which compared the effects of exercise to a sedentary control group in people with MS, as well as healthy controls. The training group received 30 sessions of progressive continuous cardiovascular and resistance exercise over 24 weeks. This cohort comprised people with RRMS and were mildly affected (mean EDSS of 2.6). The cardiovascular training started at 1 x 6 minutes per session and progressed to 3 x 10 minutes per session. Resistance training started at 1 x 10 reps of each exercise and progressed to 4 x 15 reps. Intensity for all exercise was between 12 and 14 on the Borg scale of perceived exertion and a full list of resistance exercises can be seen in Table 7-1. The authors reported that the participants with MS had a lower resting BDNF concentration compared to the healthy matched controls. The authors also reported that, at the end of the training intervention, the exercise group had a

higher resting BDNF concentration compared to the sedentary group who displayed a decrease in their resting concentration.

The controlled trial by Castellano and White (2008) compared resting BDNF levels of 11 mildly affected (mean EDSS 3.0-4.0) people with RRMS against healthy controls after eight weeks of thrice weekly training of 30 minutes at 60% of VO_2 peak (Table 7-1). The authors found that while the resting BDNF concentrations were lower in those with MS at baseline, they were not different between the two groups at the end of the intervention indicating a training effect in the MS participants but not the healthy controls.

An RCT by Bansi et al. (2013) compared aquatic cycling to on-land cycling in people with MS. This sample was moderately disabled by their MS (mean EDSS 4.7) but the MS type of participants was not reported. Both groups exercised at 60% of VO_2max five times per week for three weeks. The researchers found an increase in resting BDNF concentrations in the aquatic cycling group but not in the land-based cycling group.

The conflicting evidence for the effect of training on resting BDNF levels in people with MS indicates that further investigation is warranted in this field. While four out the six studies had cohorts that were mildly impaired and two had samples that were moderately impaired, level of disability did not appear to affect the results. However, the three studies that included people with progressive MS, either as a whole cohort (Briken et al., 2016) or within a mixed population (Schulz et al., 2004, Zimmer et al., 2017), did not report an increase in BDNF concentrations after the training interventions. These three studies would suggest that aerobic training did not have an effect on resting BDNF concentrations. However, two of these studies did not provide a power calculation (Briken et al., 2016, Schulz et al., 2004) and while one did provide a power calculation it was for cognitive testing and not BDNF (Zimmer et al., 2017). Therefore further research, with a fully powered sample, is required to deny or confirm the lack of effect of exercise training on resting BDNF levels in people with progressive MS.

7.4 Effect of exercise on blood lipids in people with Multiple Sclerosis

Lipoproteins carry cholesterol ester and fat in the form of triglyceride around the body as these substances are hydrophobic and thus non-soluble in blood (McArdle et al., 2006). Lipoproteins fall into two broad categories: High Density Lipoproteins (HDL) and Low Density Lipoproteins (LDL). The HDL are smaller and less likely to cause atherosclerosis while LDL are exponentially larger and are more likely to cause atherosclerosis (Barquera et al., 2015). Low density lipoproteins become attached to the endothelium, release cholesterol into the arterial wall and become oxidised initiating an inflammatory response (Pryor and Ammani Prasad, 2008). This attracts macrophages which ingest the LDL and become "foam cells" (McArdle et al., 2006). This in turn encourages production of smooth muscle cells which ingest some of the lipid, and also become foam cells, before being covered in a fibrous cap which gives the visual appearance of a fatty streak (Lu and Daugherty, 2015).

In early MS, high levels of HDL are associated with lower blood brain barrier permeability (Fellows et al., 2015) and low levels of HDL and high levels of total cholesterol are associated with inflammation in MS (Mandoj et al., 2015, Tettey et al., 2014, Weinstock-Guttman et al., 2011). In people with higher EDSS scores, high levels of total cholesterol, low HDL and high LDL levels are associated with poor clinical and MRI outcomes (Zhornitsky et al., 2016).

While LDL levels are considered to be a risk factor for cardiovascular disease, NICE guidelines have recommended that non-HDL cholesterol levels should instead be used a surrogate marker. This is due to ease of measurement, as LDL measurement requires a fasting sample while non-HDL cholesterol does not require fasting (NICE, 2014a). The recommended level of total cholesterol is 5 mmol/l or less. Non-HDL levels should not exceed 4.0 mmol/l, HDL levels should be 1.0 mmol or more and non-fasting triglyceride should not exceed 2.3 mmol/l (Heartuk.org.uk, 2017). A review by Wens et al. (2013) found that it was unclear whether people with MS were at risk of developing cardiovascular disease from dyslipidemia because studies measuring cholesterol, triglyceride and HDL levels produced conflicting results. An investigation into the effects of eight weeks of progressive resistance training in women with an EDSS of 4.0 found no effect on

triglyceride, total cholesterol or HDL levels (White et al., 2006). Similarly, even though physical activity is associated with lower total cholesterol and HDL levels in healthy adults, this is not necessarily true for people with MS, but physical activity may have a beneficial effect on fasting triglyceride levels (Slawta et al., 2002). Finally, a cohort trial by Keytsman et al. (2017), which investigated the effects of 12 weeks of HIIT and resistance training in people with RRMS (described in detail in section 7.13) did not report any changes in HDL, LDL, total cholesterol or fasting triglycerides. Despite these three studies there has not been an investigation into the effect of aerobic exercise on lipoprotein and cholesterol levels in people with progressive MS.

7.5 Effect of exercise on mental processing speed in people with Multiple Sclerosis

Cognitive disorders in general in MS were discussed in section 2.7.8. A recent systematic review, which included nine studies, reported that the evidence was conflicting regarding the effect of exercise training on mental processing speed in people with MS (Sandroff et al., 2016). The same review found that although evidence was limited, there was an indication for an increase in processing speed after an acute bout of exercise in people with MS (Sandroff et al., 2016).

Since this review has been published an investigation into the effects of HIIT on mental processing has been carried out. This RCT by Zimmer et al. (2017) (described later in detail in section 7.13) found that both the HIIT and continuous training groups improved their mental processing as measured by the Symbol Digit Modalities Test (SDMT) but that there was no difference between the groups.

7.6 Effect of exercise on fatigue in people with Multiple Sclerosis

Fatigue was discussed in detail in section 2.7.5. In people with MS with mild to moderate disability, fatigue is often reported as the most disabling symptom and having the largest impact on quality of life (Strupp et al., 2012, Wynia et al., 2008). A Cochrane review of studies exploring exercise in the management of

fatigue in people with MS concluded that while the evidence suggested a positive effect, it was weak, and noted the majority of studies did not target those who were fatigued or severely fatigued (Heine et al., 2015).

7.7 High Intensity Interval Training

Traditionally, exercise programmes to increase fitness and reduce cardiovascular disease risk factors entail 30-60 minutes of Continuous moderate intensity training (CONT) at 40-85% of maximal intensity, with higher intensities producing a greater increase in fitness (Pollock et al., 1998). High Intensity Interval Training, however, involves short bursts of exercise at higher intensities with either a complete or working rest in between bursts. Training sessions typically last around 20 minutes, have 4-6 cycles of 80-95% of maximal effort for 1-4 minutes with a similar time of working recovery at approximately 40% of maximal effort (Cassidy et al., 2017, Kessler et al., 2012).

Aerobic HIIT can be traced back to the 1970s, Sebastian Coe reported in his autobiography that his father developed a 200 m training regime, running 200 m repeatedly with 30 second rests in between (Coe, 2012). Later Professor Izumi Tabata, developed this further comparing CONT to high intensity sprints at 20 seconds of 170% VO_2max, with 10 seconds rests, repeated to exhaustion over approximately 8 sprints (Tabata et al., 1996). They found that VO_2max increased more in the HIIT group.

Little et al. (2010) proposed a less intensive routine of 8-12 cycles of 60 seconds at 95% VO_2max with 75 seconds rest. They found that training three times per week produced similar effects to 5 times per week of endurance training at 50-70% VO_2max. The same research group developed their protocol further for those who had never exercised, consisting of 10 intervals at 60% peak power followed by 60 seconds of recovery (Hood et al., 2011). Variations of these training programmes are recognised today as HIIT and have become popular in modern society (Fleg, 2016).

Compared to CONT, HIIT is more efficient in improving VO_2 max in healthy individuals (Milanovic et al., 2015), people with coronary artery disease (Elliott et al., 2015), increased cardio-metabolic risk (Weston et al., 2014), chronic

heart failure (Haykowsky et al., 2013, Ismail et al., 2013, Smart et al., 2013) and in older adults with chronic heart failure (Wisloff et al., 2007). The main logistical advantage of HIIT is the shorter time required to achieve similar energy expenditure and similar or greater benefits than CONT (Fleg, 2016). These benefits include improvements in aerobic fitness and cardiovascular risk factors such as body composition, blood pressure, and glucose metabolism.

7.8 Safety of High Intensity Interval Training

A recent systematic review found HIIT to be safe in people with an elevated cardiovascular risk and produced more benefits than CONT (Fleg, 2016). A meta-analysis involving people with chronic heart failure, from a total of 5877 participants, found that no deaths could be assigned to either moderate or high intensity training (Ismail et al., 2013). In addition, an analysis of participants with coronary artery disease found that major complications were one per 23,182 hours of HIIT and one per 129,456 hours of CONT (Rognmo et al., 2012). While there is no evidence to suggest that HIIT is dangerous in people with respiratory conditions there is also no evidence, at present, confirming that it is safe.

7.9 High intensity interval training in neurological disease

Previous work in people with Parkinsons found that HIIT can increase Brain Derived Neurotrophic Factor (BDNF) production and decrease parkinsonian rigidity and muscle tone (Marusiak et al., 2015), improve gait parameters (Pohl et al., 2003), and improve cognitive performance (Alves et al., 2014). In addition there is limited, but positive evidence for using HIIT to improving walking endurance in stroke survivors (Boyne et al., 2015, Boyne et al., 2016).

High Intensity Interval Training has been cited as a possible efficient training modality for people with MS as it can allow training at high intensities while avoiding thermosensitive reactions (Dalgas et al., 2008). This training modality is

however, still under researched in people with MS. In preparation of this thesis a systematic review of the literature for using HIIT in people with MS was conducted. The following sections (7.10 to 7.15) present this review which has been submitted for publication in Multiple Sclerosis and Related Disorders. This systematic review differs from the previous systematic review in Chapter 3 as this systematic review, of HIIT in MS, included studies with participants with all types of MS, while the review in Chapter 3 only included studies that focussed on people with progressive MS or separated their data by MS type.

7.10 Systematic review: Abstract

Background: Aerobic High Intensity Interval Training (HIIT) is safe in the general population and more efficient in improving fitness than continuous moderate intensity training. The body of literature examining HIIT in Multiple Sclerosis (MS) is expanding but to date a systematic review has not been conducted. The aim of this review was to investigate the efficacy and safety of HIIT in people with MS.

Methods: A systematic search was carried out in September 2017 in EMBASE, MEDline, PEDro, CENTRAL and Web of Science Core collections using appropriate keywords and MeSH descriptors. Reference lists of relevant articles were also searched. Articles were eligible for inclusion if they were published in English, used HIIT, and included participants with MS. Quality was assessed using the PEDro scale. The following data were extracted using a standardised form: study design and characteristics, outcome measures, significant results, drop-out, and adverse events.

Results: Seven studies (described over 11 articles) were identified: five randomised controlled trials and two cohort studies. PEDro scores ranged from 3-8. Included participants (n=228) were predominantly mildly disabled; one study included only people with progressive MS. Six studies used cycle ergometry and one used arm ergometry to deliver HIIT. One study reported six adverse events, four which could be attributed to the intervention. The other six reported that there were no adverse events. Six studies reported improvements in at least one outcome measure, however there were 60 different outcome measures in the

seven studies. The most commonly measured domain was fitness, which improved in five of the six studies measuring aspects of fitness. The only trial not to report positive results included people with progressive MS and a more severe level of disability (Extended Disability Status Scale 6.0-8.0).

Conclusions: HIIT appears to be safe and effective in increasing fitness in people with MS and low levels of disability. Further research is required to explore the effectiveness of HIIT in people with progressive MS and in those with higher levels of disability.

7.11 Systematic review: Introduction

Exercise is a safe and feasible intervention for people with Multiple Sclerosis (MS) (Heine et al., 2015) and is recommended for increasing cardiovascular fitness and muscular strength (Latimer-Cheung et al., 2013). Cardiovascular fitness in people with MS is lower compared to healthy individuals (Langeskov-Christensen et al., 2015) and is inversely correlated with disease severity and impairment, with fitness and conditioning decreasing as disability and fatigue rise (Heine et al., 2014, Heine et al., 2016, Kuspinar et al., 2010, Motl and Fernhall, 2012, Marrie and Horwitz, 2010, Valet et al., 2016). Reviews of trials evaluating the effects of exercise in people with MS have indicated that exercise training is beneficial for reversing deconditioning, and thus increasing cardiovascular fitness (Dalgas et al., 2008, Rietberg et al., 2005).

Traditionally, Continuous moderate intensity training (CONT) programmes, to increase fitness and reduce cardiovascular disease risk factors in healthy adults, last 30-60 minutes at 40-85% of maximal intensity, with higher intensities producing a greater increase in fitness (Pollock et al., 1998). High Intensity Interval Training (HIIT), however, involves short bursts of exercise at very high intensity with either a complete or working rest in between bursts. Training sessions typically last around 20 minutes, have 4-6 cycles of 80-95% of maximal effort for 1-4 minutes with a similar time of working recovery or rest (Cassidy et al., 2017, Kessler et al., 2012).

Compared to CONT, HIIT is more efficient in improving VO_2 max in healthy individuals (Milanovic et al., 2015), people with coronary artery disease (Elliott

et al., 2015), increased cardio-metabolic risk (Weston et al., 2014), and heart failure (Haykowsky et al., 2013, Ismail et al., 2013, Smart et al., 2013, Wisloff et al., 2007). HIIT also produces greater or equal effects, to CONT, in improving cardiovascular risk factors such as high blood pressure and altered glucose metabolism (Fleg, 2016). The main advantage of HIIT over CONT is the shorter time required to achieve similar energy expenditure, and comparable, or greater benefits (Fleg, 2016). This is due to an increase in oxygen consumption after acute strenuous exercise known as Excess Post-exercise Oxygen Consumption (Gaesser and Brooks, 1984). Furthermore, shorter exercise intervals of 2 minutes or less have been found to be more enjoyable by participants due to the shorter duration of each burst at high intensity (Cassidy et al., 2017).

Previous work examining the effect of HIIT in people with Parkinson's found an increase in Brain Derived Neurotrophic Factor (BDNF) production, decrease parkinsonian rigidity and muscle tone (Marusiak et al., 2015), improved gait parameters (Pohl et al., 2003) and cognitive performance (Alves et al., 2014). In addition there is limited but positive evidence for using HIIT to improve walking endurance in stroke survivors (Boyne et al., 2015, Boyne et al., 2016).

High intensity interval training has been recommended as a possible effective intervention for people with MS as it can allow people to exercise at higher intensities while avoiding thermosensitive reactions (Dalgas et al., 2008). Over the past several years there has been increasing interest in HIIT in MS and several interventional trials published, however no systematic review of HIIT in people with MS has been undertaken. Therefore the aim of this review was to establish the efficacy and safety of HIIT in people with MS.

7.12 Systematic review: Methods

An electronic search was undertaken of the following databases in September 2017: EMBASE, MEDline, PEDro, CENTRAL and Web of Science Core collections. The search terms used can be seen in Table 7-2 The Boolean operators 'AND' and 'OR' were used to combine searches as appropriate. No limits were placed on time of publication. The reference lists of included articles were also searched.

Articles were eligible for inclusion if they were clinical trials that consisted of aerobic HIIT as an intervention (defined as intervals of exercise of 5 minutes or less reaching an intensity of 80% or more of maximal effort in each interval (Fleg, 2016)), included participants with MS, or if in a mixed population, data for people with MS were presented separately and published in English. Articles were excluded if they were non-human studies, case studies, conference abstracts or focused solely on resistance, core or balance training. To ensure relevant articles were included, if the abstract or title did not provide the exercise intensity, the methods of the articles were read.

Table 7-2. Search strategy

Database	Search terms
Medline	((exp Multiple Sclerosis/) OR ((Multiple Sclerosis or relapsing remitting OR chronic progressive OR secondary progressive OR primary progressive).mp.)) AND ((High intensity interval training OR interval training OR High intensity interval exercise OR interval exercise OR aerobic interval training OR high intensity OR high-intensity OR exercise intensity OR HIIT OR HIT).mp.)
Embase	((multiple sclerosis/) OR ((Multiple Sclerosis or relapsing remitting OR chronic progressive OR secondary progressive or primary progressive).mp.)) AND ((High intensity interval training OR interval training OR High intensity interval exercise OR interval exercise OR aerobic interval training OR high intensity OR high-intensity OR exercise intensity OR HIIT OR HIT).mp.)
Web of Science core collections	(TS=("Multiple sclerosis" OR "MS" OR "relapsing remitting" OR "chronic progressive" OR "secondary progressive" OR "primary progressive")) AND (TS=("High intensity interval training" OR "Interval training" OR "High intensity interval exercise" OR "Interval exercise" OR "Aerobic interval training" OR "High intensity" OR “High-intensity” OR "HIIT" OR "HIT"))
PEDro	High intensity multiple sclerosis
CENTRAL	(((Multiple Sclerosis) OR (relapsing remitting) OR (chronic progressive) or (secondary progressive) OR (primary progressive)) OR (MeSH descriptor: [Multiple Sclerosis] explode all trees)) AND (((High intensity interval training) OR (interval training) or (High intensity interval exercise) OR (interval exercise) OR (aerobic interval training) OR (high intensity) OR (high-intensity) OR (exercise intensity) or (HIIT) or (HIT)))

Abbreviations: exp: explode; mp: multi-purpose keyword search; TS: Topic Search

Quality assessment was carried out using the PEDro scale which is valid and reliable in methodological rating of studies (de Morton, 2009, Maher et al.,

2003). The PEDro scale has 11 criteria but produces a score out of ten as no point is awarded for listing of exclusion and inclusion criteria. Included articles were assessed by at least two reviewers (EC, EHC, LP). Where there was disagreement between reviewers this was settled by discussion. Although primarily for randomised controlled trials, the PEDro scale can be used for cohort studies, with points deducted due to lack of randomisation. This has been done in previous systematic reviews of multiple sclerosis interventions (Kjolhede et al., 2012).

The following data were extracted from each article into a standardised form: authors, date of publication, study design, sample size, type of MS, disability level, number of drop-outs, adverse events, length of intervention, frequency of training, type of training, number of intervals per session, target intensity ranges, total time spent in high intensity during the intervention, additional training modalities employed, outcome measures and results.

7.13 Systematic review: Results

The electronic search identified 935 potential articles and hand searching of relevant reference lists provided an additional article. After the removal of 264 duplicates, the remaining 671 articles were screened by title and abstract. From titles alone, 575 were excluded. Following this, another 58 were excluded by abstract. The full text of 38 articles were read for eligibility by at least two members of the research team and 27 were subsequently excluded (Figure 7-1). Eleven articles, which described seven studies, were included in this review.

Of the included articles four were Randomised Controlled Trials (RCTs) (described by seven articles) (Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zimmer et al., 2017, Skjerbæk et al., 2014, Bansi et al., 2017), one was a randomised crossover trial (Collett et al., 2017) and two were cohort studies (Zaenker et al., 2016, Keytsman et al., 2017).

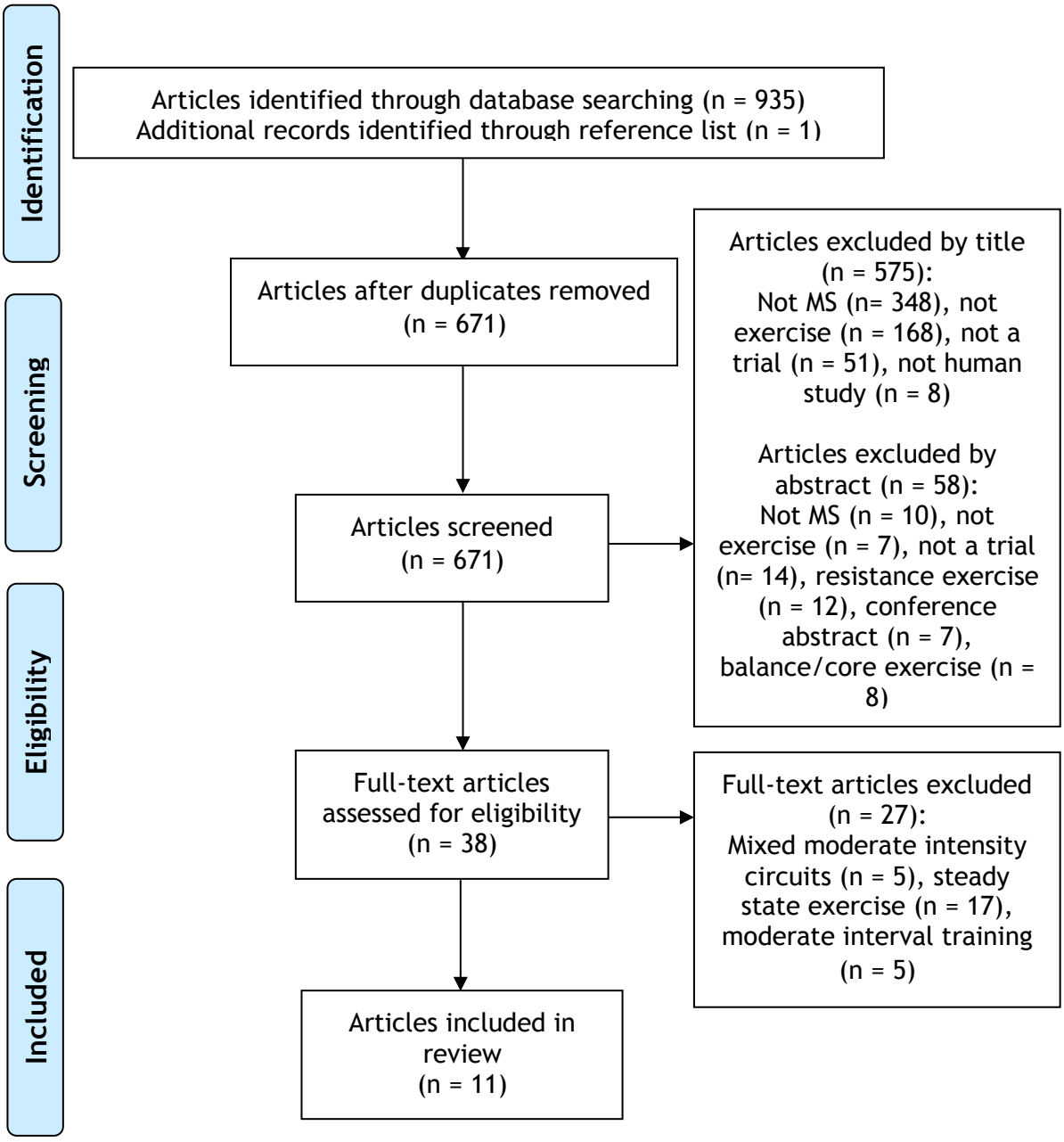

Figure 7-1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of screening and inclusion process for review (Moher et al., 2009)

Abbreviations: n: number, MS: multiple sclerosis

PEDro scores ranged from three to eight out of ten (Table 7-3). Eight articles were regarded to be of high quality with a score of seven (Bansi et al., 2017, Feltham et al., 2013, Skjerbæk et al., 2014, Wens et al., 2015, Wens et al., 2017) or eight (Collett et al., 2011, Farup et al., 2016, Zimmer et al., 2017).

Points were commonly lost due to a lack of blinding of participants and therapists. All articles were included in the review regardless of PEDro score.

Table 7-3. Quality assessment of articles using the PEDro scale

Lead author, year	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	Total
Collet, 2011	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Feltham, 2013	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7
Collet, 2017	Y	N	Y	Y	N	N	N	N	N	Y	Y	4
Wens, 2015	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Farup, 2016	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Wens, 2017	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Skjerbaek, 2014	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Zaenker, 2017	Y	N	N	N	N	N	N	Y	Y	N	Y	3
Zimmer, 2017	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Bansi, 2017	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Keytsman, 2017	Y	N	N	N	N	N	N	Y	Y	N	Y	3

C1: specification of inclusion criteria; C2: randomisation of participants; C3: concealment of allocation; C4: groups similar at baseline; C5: blinding of subjects; C6: blinding of therapists; C7: blinding of assessors; C8: one key outcome measure taken for at least 85% of sample; C9: intention to treat analysis if appropriate; C10: between group statistical analysis; C11: point measures and measures of variability

Three of the studies, reported by seven articles, provided a power calculation and had a sample size large enough to be powered (Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zimmer et al., 2017). The other four studies did not report on power (Skjerbæk et al., 2014, Collett et al., 2017, Zaenker et al., 2016, Keytsman et al., 2017, Bansi et al., 2017). Only one study had a follow up period, which was 12 weeks after completion of the intervention (Collett et al., 2011) (Table 7-4).

Sample sizes ranged from 11 (Skjerbæk et al., 2014) to 61 (Collett et al., 2011) with a total number of 249 participants. Five studies included participants that were predominantly mildly disabled (EDSS < 4.0) (Collett et al., 2011, Collett et al., 2017, Feltham et al., 2013, Keytsman et al., 2017, Farup et al., 2016, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016) one study recruited a predominantly moderately disabled group (EDSS 4.0-6.0) (Zimmer et al., 2017, Bansi et al., 2017) and one study recruited participants who were more severely

disabled (EDSS 6.0-8.0) (Skjerbæk et al., 2014) (Table 7-4).Five studies included participants with both Relapsing Remitting MS (RRMS) and progressive MS (Bansi et al., 2017, Collett et al., 2011, Collett et al., 2017, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zimmer et al., 2017), one study only included participants with progressive MS (Skjerbæk et al., 2014), and one study did not report on MS type (Keytsman et al., 2017).

All studies conducted HIIT, in a supervised setting, on a cycle ergometer apart from Skjerbæk et al. (2014) who used upper limb ergometry. Four studies (eight articles) compared HIIT to a form of continuous training (Bansi et al., 2017, Collett et al., 2011, Collett et al., 2017, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zimmer et al., 2017), one study compared HIIT and in-patient rehabilitation to just in-patient rehabilitation (Skjerbæk et al., 2014), and two studies did not have a comparator group (Keytsman et al., 2017, Zaenker et al., 2016) (Table 7-4).

Four studies (eight articles) combined HIIT with another form of exercise training; two with resistance training (Farup et al., 2016, Wens et al., 2015, Wens et al., 2017, Keytsman et al., 2017), one with CONT (Collett et al., 2011, Feltham et al., 2013), and one with both resistance training and CONT (Zaenker et al., 2016) (Table 7-4).

In terms of exercise dose, the number of training sessions ranged from 1 to 30 and length of intervention ranged from 3 weeks (Bansi et al., 2017, Zimmer et al., 2017) to 12 weeks (Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Keytsman et al., 2017). Length of exercise interval ranged from 30 seconds (Collett et al., 2011, Collett et al., 2017, Feltham et al., 2013) to 2 minutes (Farup et al., 2016, Keytsman et al., 2017, Wens et al., 2015, Wens et al., 2017). One study had intervals of 3 minutes but only 30-60 seconds of each was spent at a high intensity (Skjerbæk et al., 2014). Total time spent in high intensity exercise, over the whole intervention, ranged from 10 minutes (Collett et al., 2017) to 225 minutes (Farup et al., 2016, Keytsman et al., 2017, Wens et al., 2015, Wens et al., 2017) (Table 7-4).

Table 7-4 Summary of evidence of high intensity interval training in people with MS

Author, Year, Design	n, Drop-outs, Powered	MS type, Disability	Intervention	Outcome Measures, Time points	Statistically significant results*
Collett et al. 2011 RCT 3 arm	n=61 Drop out: 6 Pow: Y	RR: 22 SP: 25 PP: 7 Unknown: 1 Barthel index: 19 Able to walk 2min with or without aid	HIIT vs CONT vs COMB 12 wks, 2/wk Total: 24 sessions CONT (n=20): 45% peak power, 20 min HIIT (n=18): 90% peak power 30sec on 30 sec off, 20 min COMB (n=17): 10 min CONT a/a followed by 10 HIIT a/a	2 min walk TUG Leg ext power Peak power Barthel Index SF36 FSS 0, 6, 12, 24 wks	2 min walk (WG) (p<0.01) 6 wks: HIIT: +12.94m (4.71), CONT: +4.71m (4.24), COMB: +3.22m (4.60). Improvements maintained at 24 wks TUG (WG) (p<0.05) 6wks: HIIT: -2.5s (1.8), CONT: -3.5s (1.7), COMB: -0.9s (1.9). Improvements maintained at 12 wks but not 24 Leg power (ALL) (p<0.01) 6 wks: +19.4W (4.1), 12 wks: +15.9W (4.1), 24 wks: -10.9W (3.1) Peak power (ALL) (p<0.05) 24 wks: -29W (5) SF36: (p<0.05), 12 wks: -4.5 (1.6) maintained at 24 wks
Feltham et al. 2013	Sub-analysis of Collett et al.	RR: 9 SP: 9 PP: 3	CONT a/a n=12 HIIT a/a n=9	BP RER Peak power	VO_2 peak (ALL) (p =0.05): increase from med 8.05ml/kg (2.23) to med 9.2ml/kg (3.72)

RCT	2011 n=21	 Barthel index: 19 Drop out: 0		VO_2 max VO_2 norm HRMax 0, 6, 12 wks	 Peak power (ALL) (p =0.05): increase from med 112W (58) to med = 113W (55)
Collett et al. 2017 RXT	n=23 14 with MS 9 HC Drop out: 4 (3 MS, 1 control) Pow: N	RR: 5 SP:5 PP:1 Barthel index: 19 (1) Able to use ergometer safely	CONT1 vs CONT2 vs HIIT 3 weeks, 1 session/week Each participant did as single CONT1, CONT2 and HIIT session CONT1: 20 min 45% peak power CONT2: 20 min 60% peak power HIIT: 20 min 90% peak power (30 sec intervals with 30 sec rest)	Recovery of: HR, Temp, RPEbr, RPEleg, MEPs 30 sec post session then every 2 min till 10min, then every 5 min till 45 min	Return to resting HR: CONT1: MS in 15 min vs control 4 min CONT2: both groups not down to rest HR in 45 min HIIT: both MS and control return in 30 min Recovery to baseline RPEleg CONT1: MS 6 min vs control 0.5 min CONT2: MS 15 min vs control 6 min HIIT: MS 35 min vs control 4 min RPEbr: CONT1: MS 8 min vs control 0.5 min CONT2: MS 6 min vs control 2 min HIIT: MS 6 min vs control 6 min MEP: Return to baseline levels; CONT1: both groups in 15 min CONT2: MS 15 min vs control 25 min HIIT: MS MEP not significantly decreased and control recovered in 4 min

					Temp: CONT1: no change CONT2: MS group returned to baseline in 35 min, no change in control HIIT: MS group returned baseline in 25 min, control in 8 min.
Wens et al. 2015 RCT 3 arm	n=34 Drop out: 0 Pow: Y	RR: 26 Progressive: 8 (type of progressive NR) EDSS range 1.0-6.0 Mean EDSS 2.7	SED vs HIIT+RES vs CONT+RES 12 wks, 5 session/2 wks SED, n=11: no intervention HIIT+RES, n=12: 5 x 1 min peak power (80-90%HRMax)for 6 weeks 5 x 2 min 100-120% peak power (90-100% HRMax) 6 weeks CONT+RES, n=11: 6 min at 80-90% HRMax for first 6 weeks For second 6 weeks progressed to 2 x 10 min at 90-100% HRMax RES for both ex groups:	Muscle fibre CSA and proportion Isometric muscle strength Endurance capacity: RER VO_2max HRMax Test duration Body composition PA level; PASIPD	BG compared to SED: Mean CSA muscle fibres HIIT: +21% (7) (p<0.05) CONT: +23% (5) (p<0.01) Muscle fibre type I CSA: CONT: +29.8% (5.5) (p=0.003) Muscle fibre type IIa CSA: HIIT: 22.8% (6.2) (p<0.05) BG compared to SED: Strength knee flex + ext weak leg: HIIT: range +24% (13) to +44% (20) (p= 0.01 to p=0.006) CONT: range +19% (9) to 33% (17) (p= 0.01 to p=0.006) Hams strong leg HIIT: range +13% (7) to +20% (7) (p=0.006)

			leg presses, curls, extensions, lateral pull downs, arm curls, chest presses. Intensity 1 x 10 reps max load, progressed to 2 x 20 reps max load	0, 12 wks	BG compared to SED and CONT: Peak power +21% (4) (p = 0.0001) Time to exhaustion +24% (5) (p=0.00008) VO_2max +17% (5) (p=0.001) Lean tissue mass (WG): HIIT + 1.4% (0.5) (p = 0.01) Body fat percentage (WG) HIIT: -3.9% (2) (p = 0.04) CONT: -2.5% (1.2) (p = 0.02) HRMax (WG) CONT: +3.7% SD1.5 HIIT: +6.2% SD 2.2 PASID (BG vs SED) HIIT: 86% (27) (p = 0.004) CONT: 73% (19) (p = 0.003)
Wens et al. 2017 Same as Wens et al. 2015	Same as Wens et al. 2015	Same as Wens et al. 2015	Same as Wens et al. 2015	AUC from OGTT Fasting glucose conc GLUT4 content vastus lateralis	All WG: Fasting glucose conc HIIT: -7.3% (6.8) (p< 0.05) CONT: - 9.0% (6.2) (p< 0.05) Glucose clearance (AUC) HIIT: -6.9% (6.2) (p< 0.05) CONT: -11.0% (7.7) (p< 0.05)

					Insulin (AUC) CONT: -12.3% (14.7) (p< 0.05) Muscle GLUT4 content: HIIT: +6.6% (4.5) (p< 0.05)
Farup et al. 2016 Same as Wens et al. 2015	Same as Wens et al. 2015 but no SED group HC n=18 Pow: Y	MS mixed no SED group	Combined exercise groups as Wens et al 2015 No SED group	SC/type I fibre SC/type II fibre, SC/ mm^2 type I and II fibre Myonuclei, and central nuclei analysis Muscle tissue fibrosis and lipid content	MS(WG): SC/type II fibre: +165% (68) (p<0.05) SC/mm2 type II fibre: +135% (63) (p< 0.05) Lipid content BG MS vs HC MS: +117% (37) (p < 0.05).
Zaenker et al. 2017 Cohort study	n=26 Drop out: 0 Pow: N	MS mix RR 22 SP 3 PP 1 EDSS med 2.0 (0-5)	HIIT+RES+CONT 12 wks Wks 1-4: 1 x HIIT and 1x RES session/wk Wks 5-12: a/a + unsupervised CONT or RES session HIIT: 10 min warm up, 5 x 1 min 90-110% peak power, 3	VO_2 peak Peak power Peak lactate HRMax Isokinetic strength quads and hams	ALL WG as cohort study VO2peak +13.5% (p<0.0001) Peak power +9.4% (p<.0001) Peak lactate +31% (p<0.001) HRMax +3.73% (p=0.0120) Inc strength quads and hams at all torques (p<0.05) (size of change not provided) SEP 59: Improvement in vitality (p=

			min working rest, 5 min warm down RES: body weight exercises, 2 x hams + 2 x quads. Start 4 x 10 reps prog to 5 x 15 reps CONT: 30-45 min CONT of pt choice such as cycling, swimming or walking	QoL: SEP 59 0, 12 wks	0.0012), emotional well-being (*p*= 0.0378), and general well-being (*p*= 0.0052) size of change not reported.
Zimmer et al. 2017 RCT	n=57 Dropout: 3 Pow: Y	MS mix RR (30) and SP (27) EDSS range 1.0-6.5 Mean 4.37	HIIT vs CONT 3 Weeks, HIIT 3 x week, CONT: 5 x week HIIT: 20 min, 5x 3 min intervals at 85-90% of HRMax, with 1.5 min working rest at 50-60% HRMax CONT: min 70% HRMax	BICAMS: TMT, TAP test (errors and speed), SDMT, VLMT, BVMT Serum levels of serotonin, BDNF, MMP-2, MMP-9, VO_2peak 0, 3 wks	Time effects SDMT TMT TAP errors Time x group effect Serum MMP-2 in HIIT: decreased *p*=0.009 CI (5.336; 36.587) CONT: no change *p*=0.305 CI (-22.470; 7.169) VO2 peak in both groups HIIT: *p*<0.001 CI (-4.096; -2.002) CONT: *p*=0.006 CI (-2.394; -0.426) VLMT

					HIIT: improvement *p*=0.046 (CI) (-6.319; -0.51)) CONT: no change *p*=0.316 CI (-1.473; 4.473)) TAP errors HIIT improved *p*=0.001 CI (0.508; 1.789) CONT: p=0.327 CI (-0.308; 0.908)
Bansi et al. 2017 Same as Zimmer et al. 2017	Same as Zimmer et al. 2017	Same as Zimmer et al. 2017	Same as Zimmer et al. 2017	HIIT vs CONT: within RRMS and SPMS 5HT,Trp, Kyn, Kyn/Trp ratio	RRMS training groups (no diff between HIIT or CONT): Reduction in Trp (*p*=0.02) Increase in Trp/Kyn ratio (*p*=0.002)
Skjerbaek et al. 2014 RCT	n=11 Drop out: 1 Pow: N	PP (n=3) SP (n=8) EDSS 6.5-8.0	HIIT + in-pt rehab vs in-pt rehab 10 sessions over 4 wks, UL ergometer HIIT training 6x 3 min intervals: 2min at 65-75%VO2max followed by 30-60 sec sprint of 100% max effort	Pri: VO_2 peak, HRMax, 6minWC, FSMC, MDI, MSIS-29, 9HPT, HGT, BBT 0, 4 wks	Nil
Keytsman et al. 2017 Cohort study	n=16 Drop out: 0 Pow: N	MS type: NR EDSS mean 2.6	HIIT+RES 12 wks, 5 session per 2 wks HIIT Wks 1-6: 5 x 1min 85-90% HRmax, 1 min rest Wks 7-12: 5 x 2min 100% HRmax, 1 min rest RES: leg presses, curls,	Body composition, resting HR, BP, OGTT, total chol, fasting glucose,	All *p*<0.05 Resting HR: -6% (bpm) 2 hr glucose conc: -13% (mmol/l) Insulin sensitivity: -24% WMax; +25 W (CI -34, -16) t to exhaustion: +2 min (CI-3,-1)

			extensions, lateral pull downs, arm curls, chest presses. Intensity 1 x 10 reps max load, progressed to 2 x 20 reps max load after 6 wks	fasting TG, HDL, LDL, insulin sensitivity, Wmax, HRMax, VO_2max, RER, peak lactate, t to exhaustion, VEmax Isometric and isokinetic strength of legs ext and flex, PASID	VEmax: 15 l/min (CI-23,-7) Isometric and isokinetic strength increased in both legs Peak lactate +2.1 mmol/l RER: -0.04 VO_2max: +5.9 ml/min/kg

Abbreviations: RCT: randomised controlled trial; RXT: randomised crossover trial; n: number of participants; Pow: statistically powered; a/a: as above; HC: healthy controls; RR; relapsing remitting; SP: secondary progressive; PP: primary progressive; min: minute; NR: not reported; EDSS: expanded disability status scale; HIIT: high intensity interval training; SED: sedentary; med: median; CONT: continuous moderate intensity training; COMB: combination; wk: week; sec: second; RES: resistance training; HRMax: maximal heart rate; VO_2max: maximal volume oxygen consumed VO_2: volume of oxygen consumed; TUG: timed up and go test; ext: extension; SF36: short form 36; FSS: fatigue severity scale; BP: blood pressure; RER: respiratory exchange ratio; HR: heart rate; temp: temperature; RPEbr: borg scale of perceived exertion breathing; RPEleg: borg scale of perceived exertion legs; MEPs: motor evoked potentials; CSA: cross sectional area; PASIPD; Physical Activity Scale for Individuals with Physical Disabilities; OGTT: oral glucose tolerance test; conc: concentration; SC: satellite cells; quads: quadriceps; hams: hamstrings; SEP: Sclerose En Plaques-59; BICAMS: brief international cognitive assessment for MS; TMT: trail making test; TAP: Test of Attentional Performance; SDMT: symbol digit modalities test; VLMT: California verbal learning memory test; BVMT: Brief visuospatial memory test-revised; BDNF: brain derived neurotrophic factor; MMP: matrix metalloproteinases; 6minWC: 6 minute wheelchair test; 5HT: serotonin; Trp; tryptophan; Kyn; kynurenine; FSMC: fatigue scale of motor and cognitive function; MDI: major depression inventory; MSIS-29: multiple sclerosis impact scale; 9HPT: 9 hole peg test; HGT: hand grip test; BBT: box and block test; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglyceride; chol: cholesterol; VEmax: maximal expiratory volume W: watts; WG: within group analysis; BG: between group analysis: CI: confidence interval
*All values mean (standard deviation) unless otherwise stated.

One study reported six adverse events (Collett et al., 2011, Feltham et al., 2013). Four were knee or leg pain while cycling, which were deemed to be possibly related to the intervention. Two of the adverse events were unrelated to the intervention (one exacerbation of symptoms and one loss of consciousness). The other six studies reported that there were no adverse events in either their intervention or control groups (Bansi et al., 2017, Collett et al., 2017, Farup et al., 2016, Keytsman et al., 2017, Skjerbæk et al., 2014, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Zimmer et al., 2017).

The retention of participants within the studies was high; one study had a drop out of greater than 10% (Collett et al., 2017), two studies less than 10% (Bansi et al., 2017, Collett et al., 2011, Feltham et al., 2013, Zimmer et al., 2017), while four studies had no drop outs (Farup et al., 2016, Skjerbæk et al., 2014, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Keytsman et al., 2017) (Table 7-4).

A total of 60 different outcome measures were used across the seven studies. The most common domains assessed were cardiorespiratory fitness which was measured in six of the seven studies (Bansi et al., 2017, Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Keytsman et al., 2017, Skjerbæk et al., 2014, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Zimmer et al., 2017) and strength which was measured in four (Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Keytsman et al., 2017) (Table 7-4). Five of the six studies that assessed fitness found an improvement however different outcome measures were used across the studies. All four studies that measured strength reported an improvement.

Six studies measured either VO_2peak or VO_2max (Bansi et al., 2017, Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Keytsman et al., 2017, Skjerbæk et al., 2014, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Zimmer et al., 2017). One of the RCTs reported an improvement in VO_2max in their HIIT group (+17% (SD) 5, p<0.01) (Farup et al., 2016, Wens et al., 2015, Wens et al., 2017). Two RCTs reported an improvement of VO_2peak in both their HIIT and CONT groups ((median 8.05 ml/kg - 9.2 ml/kg (Collett et al., 2011, Feltham et al., 2013)), (HIIT (95% CI (–4.096; –2.002) p<0.001), CONT (95%

CI (–2.394; –0.426) p=0.006) (Zimmer et al., 2017, Bansi et al., 2017)). The two cohort studies found improvements, one in VO_2peak (+13.5% (p<0.0001) (Zaenker et al., 2016), and the other in VO_2max (+5.9 ml/min/kg (p<0.05 (Keytsman et al., 2017)). Conversely, one RCT reported no change in the VO_2peak of their HIIT group (Skjerbæk et al., 2014) (Table 7-4).

Two of the five studies which measured HRMax found significant increases in their HIIT group; (+3.73%, p=0.012 (Zaenker et al., 2016), +6.2%, p=0.05 (Farup et al., 2016, Wens et al., 2015, Wens et al., 2017)). The other three studies which measured HRMax did not find changes after their HIIT intervention (Collett et al., 2011, Feltham et al., 2013, Skjerbæk et al., 2014, Keytsman et al., 2017) (Table 7-4).

Peak power, was measured in four studies (Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Keytsman et al., 2017, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016). One RCT reported an increase in peak power after the intervention (+21% (SD 4) (p<0.01) (Farup et al., 2016, Wens et al., 2015, Wens et al., 2017)) and the two cohort studies also reported an increase in peak power (+9.4%, p<0.0001, (Zaenker et al., 2016), +25 W (CI -34, -16), p<0.05 (Keytsman et al., 2017)). The RCT by Collett et al. (2011) initially found no differences in peak power post intervention, however, subsequent analysis demonstrated that peak power was increased in participants who completed more than 8 sessions, (median 112 W to median 113 W, p=0.05) (Feltham et al., 2013) (Table 7-4).

Two cohort studies measured peak lactate and found increases after their interventions (+31%, p<0.001 (Zaenker et al., 2016), +2.1 mmol/l, p<0.05 (Keytsman et al., 2017)). One study measured endurance using the 2 min walk test and reported improvements in all groups (HIIT, CONT and combined) with the largest improvement in the HIIT group (HIIT: +12.94 m (SD 4.71), CONT: +4.71 m (SD 4.24), combined: +3.22 m (SD 4.60), p<0.01) and all improvements were maintained at 12 week follow up (Collett et al., 2011, Feltham et al., 2013) (Table 7-4).

All four studies that examined muscle strength reported improvements following the intervention (Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013,

Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Keytsman et al., 2017). Collett et al. (2011) and Feltham et al. (2013) reported improvements in isometric leg extension power at the end of the intervention but this was not maintained at a 12 week follow up (12 weeks: +15.9W SD 4.1, 24 weeks: -10.9W SD 3.1, $p<0.01$). One study found an increase in isometric hamstring strength in the HIIT group only (range +13% Nm, (SE 7) to +20% (SE 7), $p=0.006$) and between group differences in the quadriceps and hamstring of the weak leg in both the HIIT (range +24% Nm, SE 13, $p=0.01$, to +44% Nm, SE 20 $p=0.006$) and high intensity continuous groups (range +19% Nm, SE 9 $p= 0.01$, to 33% Nm, SE 17 $p=0.006$) (Wens et al., 2015). Both cohort studies found improvements in muscle strength (Keytsman et al., 2017, Zaenker et al., 2016). Keytsman et al. (2017) reported stronger isometric hamstring contractions in the stronger leg at 90 degrees, in quadriceps at 45 degrees, and both muscle groups in maximal isokinetic contractions. In the weaker leg stronger isometric hamstring and quadriceps contractions were found at both 45 and 90 degrees along with stronger hamstring isokinetic contractions ($p<0.05$). Zaenker et al. (2016) reported increases in the strength of quadriceps and hamstrings of both legs at three different torques of 90, 180 and 240 degrees per second ($p<0.05$) (Table 7-4).

In terms of cardiometabolic risk factors, improvements were reported in resting heart rate (Keytsman et al., 2017), glucose tolerance, physiological characteristics of muscle fibres, and body composition (Farup et al., 2016, Wens et al., 2015, Wens et al., 2017). One study observed a decrease in matrix metalloproteinase 9 concentrations, improvements in mental processing and cognition, and also differences between participants with RRMS and progressive forms of MS, but not between HIIT or CONT, in levels of tryptophan and the ratio of tryptophan to kynurenine (Zimmer et al., 2017, Bansi et al., 2017). Finally, two studies measured quality of life with conflicting results (Collett et al., 2011, Feltham et al., 2013, Zaenker et al., 2016). Full details of these results are presented in (Table 7-4).

7.14 Systematic review: Discussion

This was the first systematic review for the use of HIIT in MS. Overall, the seven studies included in the review provided positive evidence for the use of HIIT in people with MS. All studies except one (Skjerbæk et al., 2014) found improvements in multiple outcome measures. Predominantly improvements were observed in outcome measures relating to fitness. High intensity interval training was well tolerated with adverse events only occurring in one study (Collett et al., 2011, Feltham et al., 2013). Previous research has shown that HIIT is safe in healthy individuals (Milanovic et al., 2015), people with chronic heart failure (Smart et al., 2013), coronary artery disease (Elliott et al., 2015), and increased cardio-metabolic risk (Weston et al., 2014). Due to the low incidence of adverse events this review suggests that HIIT is also safe in people with MS.

The evidence in this review is positive for the use of HIIT in increasing cardiovascular fitness in people with MS. Five of the six studies that measured cardiovascular fitness reported improvements in at least one outcome measure (Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Zimmer et al., 2017, Bansi et al., 2017, Keytsman et al., 2017). Skjerbæk et al. (2014), who measured both VO_2peak and HRMax, did not find statistically significant changes, although a trend towards statistical significance for VO_2peak was reported (p=0.06, data not in Table 7-4). This study however differed from the others as the participants had progressive MS and were the most disabled and deconditioned. Furthermore, the study was underpowered and had one of the lowest time exercising at high intensity over the whole intervention (60 minutes). A similar low time at high intensity was used by Zaenker et al. (2016), but with the addition of CONT and resistance training elements to the intervention.

Skjerbæk et al. (2014) was also the only study to use arm ergometry, whereas the other studies used cycle ergometry. Arm ergometry is a practical modality of exercise for those with mobility problems but engages smaller muscles than cycle ergometry, resulting in lower energy expenditure and thus creating less demand on the cardiorespiratory system. Indeed, a previous study comparing arm ergometry, cycling and rowing at a moderate intensity in people with progressive MS, found that the cycling group increased their VO_2max while no

changes were found in the arm ergometry and rowing groups (Briken et al. 2014). Further research is warranted to investigate the efficacy of using upper limb ergometry for delivering HIIT for people with higher levels of disability/progressive MS.

Previous research comparing HIIT to CONT in other conditions has quantified the effectiveness via meta-analyses. For example, in healthy individuals HIIT is more effective than CONT in increasing VO_2max by 4.5 ml/kg/min (Milanovic et al., 2015) and in people with increased cardiometabolic risk HIIT is more effective in increasing VO_2peak by 3.03 ml/kg/min (Weston et al., 2014). While the evidence for HIIT in people with MS is positive, due to the heterogeneity of outcome measures and the lack of control groups in two of the studies, a meta-analysis was not possible or appropriate. This makes comparison of the effect of HIIT between MS and other conditions difficult.

The shortest intervention which led to an improvement in fitness was three weeks in length (Bansi et al., 2017, Zimmer et al., 2017). This trial trained the HIIT group three times per week for three weeks with a total of 135 minutes spent exercising at a high intensity. Furthermore this was the only trial to compare a HIIT programme to a CONT programme of equal energy expenditure by training five times per week. All other protocols included in this review that implemented an active comparison group of CONT, due to Excess Post-exercise Oxygen Consumption, would have resulted in greater energy expended during the HIIT protocol (Collett et al., 2011, Collett et al., 2017, Feltham et al., 2013). One other study (published over three articles) however, included a high intensity continuous group which spent 330 minutes at a high intensity (compared to 225 in the HIIT group), but it is unclear if this was to equate energy expenditure between the two groups (Farup et al., 2016, Wens et al., 2015, Wens et al., 2017). Two trials had the shortest work-time at high intensity (60 minutes), one of which reported an improvement (Zaenker et al., 2016) and one which did not (Skjerbæk et al., 2014). The trial by Zaenker et al. (2016) was a cohort study in which the intervention comprised separate sessions of HIIT, CONT and resistance training which made it difficult to attribute improvements specifically to HIIT. The lack of significant results from Skjerbæk et al. (2014) may indicate that more than 60 minutes at high intensity is needed to increase fitness in people with MS. The length of the high intensity interval did not

appear to have an impact on results as improvements in fitness were observed in the trials that used the shortest interval of 30 seconds (Collett et al., 2011, Feltham et al., 2013) and the longest interval of three minutes (Bansi et al., 2017, Zimmer et al., 2017). Therefore this may indicate that improvements in fitness in people with MS can be elicited from a lower number and frequency of HIIT sessions, compared to CONT, and that this can be achieved in as little as three weeks from a total high intensity work-time of 135 minutes. As lack of time is a cited barrier for exercise in people with MS (Asano et al., 2013) and HIIT is reported to be more enjoyable than CONT (Bartlett et al., 2011) this makes HIIT a suitable programme for exercise prescription in people with MS.

All four studies that measured muscle strength reported improvements (Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Keytsman et al., 2017). One of these did not specifically include a resistance training element (Collett et al., 2011, Feltham et al., 2013), but still reported an increase in isometric muscle strength. This may indicate that aerobic HIIT could be effective in increasing leg muscle strength however this requires further investigation.

Only one study (published over two articles) examined the effect of HIIT on neurochemicals related to MS, exploring the effects of HIIT on levels of serotonin, BDNF, metalloproteinase 2 and 9, and tryptophan metabolism (Bansi et al., 2017, Zimmer et al., 2017). The researchers reported, that compared to the CONT group, the HIIT group improved their level of matrix metalloproteinase 2. As the intervention and control undertook an exercise programme of equal energy expenditure this suggests that higher intensity of exercise could have a more beneficial effect neurological markers. The cohort study by Keytsman et al. (2017) measured the effect of HIIT on lipid profiles but did not report any significant changes (Keytsman et al. (2017). This trial was however, underpowered and had no control group. Both of these areas of research warrant further investigation, particularly since a previous review concluded that the evidence was inconclusive for the effect of aerobic exercise on BDNF in people with neurological conditions (Mackay et al., 2017) and previous work on the effect of exercise on blood lipids in people with MS was also inconclusive (Wens et al., 2013).

7.14.1 Limitations

The heterogeneity of the outcome measures used across the seven studies limited comparison with previous reviews of HIIT in other conditions and prevented a meta-analysis. The lack of power calculations in some studies also limited the applicability of results in this patient population.

7.15 Systematic review: Conclusions

The evidence presented in this review suggests that HIIT, via cycle ergometry, is a safe and effective way of improving fitness in people with MS and requires fewer, shorter training sessions compared to a moderate intensity, continuous training mode to gain benefits. Further investigation of HIIT is required in people with progressive MS and/or those with a moderate and severe level of disability. In addition, future research should examine the possible benefits of HIIT in people with MS, beyond cardiovascular fitness and muscle strength.

7.16 Summary of chapter

In summary the evidence base for using aerobic exercise to increase resting BDNF levels in people with MS suggests that there is no effect in people with progressive MS, but a lack of statistical power in previous studies limits this statement. The evidence base for using exercise to influence mental processing speed in people with MS is also inconclusive, as is fatigue. The effect of aerobic exercise on blood lipid levels in people with MS has only been examined by one study which found no effect but had methodological limitations. Therefore these areas warrant further research.

From the systematic review it was concluded that the evidence for using HIIT in people with MS suggests that is safe and has a positive effect on fitness. However, there were gaps in the research, namely in lack of studies focussing on

people with progressive MS and in people with either a moderate or severe level of disability. While the evidence suggests a positive effect on fitness the effect on other outcomes is less clear mainly due to the heterogeneity of domains assessed and outcome measures used.

Chapter 8 High intensity interval training in people with progressive Multiple Sclerosis, a feasibility trial

From the systematic review of the literature and of the literature surrounding exercise and Multiple Sclerosis (MS), gaps were identified that justified further research. These were:

- No study has focussed on High Intensity Interval Training (HIIT) in people with progressive MS and a moderate level of disability (Extended Disability Status Scale (EDSS) 4.0-6.0)
- No study has focussed on people with progressive MS and used cycle ergometry to deliver HIIT
- The effect of aerobic training on Brain Derived Neurotrophic Factor (BDNF) levels remains unknown in people with MS and in particular progressive MS
- There is conflicting evidence for the effect of HIIT on quality of life and impact of disease in people with MS

This chapter will outline the aims and objectives of a randomised controlled feasibility trial before describing the protocol. The results of the trial will be presented, discussed and compared to previous HIIT and exercise research in MS. The limitations of the trial will then be discussed, before making recommendations for future research.

8.1 Aims and objectives

The aim of this study was to evaluate the feasibility of delivering HIIT to people with progressive MS with a moderate level of disability and to evaluate the effects of HIIT, compared to Continuous moderate intensity training (CONT), on physiological and MS clinical outcomes.

The primary objective of this study was to investigate the feasibility of carrying out HIIT, twice per week for eight weeks in people with progressive MS and an EDSS of 4.0-6.0. The aspects of feasibility that were measured were tolerance to protocol, adherence by percentage of training sessions completed, compliance rate with protocol, and participant drop-outs (Bowen et al., 2009).

The secondary objectives were to compare in people with progressive MS, objectively measured physiological and clinical outcomes in those who received an eight week HIIT intervention and active controls who received a CONT intervention.

8.2 Study design and ethical approval

A Randomised Controlled Trial (RCT) design was used. A feasibility study was conducted as it was yet unclear if HIIT could be carried out in people moderately disabled by progressive MS, and how well it would be tolerated. Furthermore, the outcomes of the feasibility study were to inform a protocol for a larger powered RCT. Ethical approval for the study was granted by the West of Scotland Research Ethics Committee in January 2017 (Appendix 6) and approved by NHS Ayrshire and Arran Research and Development department in February 2017 (Appendix 7).

8.3 Recruitment

A convenience sample of people with MS was recruited from the MS Service within NHS Ayrshire & Arran. Potential participants were identified from active caseloads and discharge lists by members of the MS Service team. Posters were placed in waiting areas of the Douglas Grant Rehabilitation Centre (Appendix 8) and local MS Society support groups. The PhD student also presented to local support groups to raise awareness. Potential participants were given a participant information sheet by a member of the NHS Ayrshire & Arran MS team (Appendix 9) and were able to opt-in by contacting a member of the research

team or, if they gave written consent, their contact details were passed to the research team. The recruitment period lasted for 16 weeks. It was expected that at least one participant would be recruited per week. Therefore, it was expected that between 16 and 20 participants would, in total, be recruited.

8.4 Inclusion and exclusion criteria

Inclusion criteria for taking part in the study were:

- Having a progressive form of MS
- An EDSS score of 4.0-6.0
- Aged 18 years or older
- Known to the MS service team of NHS Ayrshire & Arran
- Able to attend the Douglas Grant Rehabilitation Centre twice a week for eight weeks
- Able to cycle safely, free of assistance on a cycle ergometer

Previous HIIT studies in MS have included participants with a predominantly low level of disability (EDSS<4.0) (section 7.13). Therefore an EDSS range of 4.0-6.0 was chosen to focus on those with a higher level of disability compared to previous research.

Exclusion criteria were:

- A relapse of symptoms requiring treatment within the past three months
- Having commenced, or had a change in, MS disease modifying treatment within the past three months
- A musculoskeletal injury or condition that could be aggravated by cycling
- A respiratory condition that could be exacerbated by high intensity exercise including chronic obstructive pulmonary disorder, uncontrolled or poorly controlled asthma.
- Uncontrolled high blood pressure at screening ($\geq$190/100 mmHg) from the average of two readings

- Cognitive impairment that would impact capacity to consent or ability to follow instructions, as noted from the participant's patient notes
- Taking part in another interventional trial or any other study that could affect their physiological or cardiovascular response to exercise
- Weighing more than 100 kg
- A cardiovascular event in the past year including but not limited to: transient ischaemic attack, cerebrovascular event and myocardial infarction.
- Condition or medical intervention that precluded taking part in high intensity exercise, maximal exertion testing, or could attenuate the cardiovascular effect of exercise including: unstable angina, diabetes, peripheral vascular disease or intermittent claudication, a pace-maker or medicine pump, surgical clips, another neurological condition other than MS, and pregnancy.
- Taking any of the following medication: beta blockers, vasodilators, ACE inhibitors, diuretics or any other medication that could cause exercise induced hypotension or hypoglycaemic agents including insulin and/or oral hypoglycaemic drugs.

While there is no evidence to suggest that HIIT is unsafe in people with cardiorespiratory conditions, such as chronic obstructive pulmonary disorder there is, at present, no evidence to say that it is safe. Thus the decision was taken to exclude participants with these conditions. Participants were excluded if they had uncontrolled high blood pressure because high intensity aerobic exercise can increase blood pressure and this would put the participant at further risk. For the same reason, participants were excluded if they had a serious cardiovascular event in the past year. A weight limit of 100kg was placed on participants as this was the weight limit of the cycle ergometer.

8.5 Screening, consent and baseline assessment

All screening, testing and training sessions were conducted by the PhD student in the Douglas Grant Rehabilitation Centre in Irvine, NHS Ayrshire & Arran. At the

initial visit, the purpose of the study was explained to the participant and they were given an opportunity to ask questions. Participants then underwent screening for eligibility (see inclusion and exclusion criteria in previous section) and provided written informed consent to participate in the study (Appendix 10) and also for their GP to be informed of their participation (Appendix 11). The participant and the researcher each kept a signed consent form and one was placed in the participant's medical notes. Participants were informed that they were free to withdraw from the study at any point.

If the participant passed the screening and gave full informed consent the following outcome measures were taken, as a baseline assessment, in the following order: blood pressure (values taken from screening measurements), resting heart rate, timed 25 foot walk test, MSIS-29 version 2, Hospital Anxiety and Depression Scale (HADS), Symbol Digit Modalities Test (SDMT), Fatigue Scale of Motor and Cognitive functions (FSMC), blood samples for resting serum BDNF concentration, resting lactate concentration, resting lactate concentration, Maximal Heart Rate (HRMax) from a graded exercise test and peak lactate concentration. These outcome measures are described in detail in sections 8.7 and 8.8. Assistance was provided with scribing if required in the self-report outcome measures. All outcome measures were taken again 3 days after the final training session in week 9. Where possible, pre and post intervention assessments were taken at the same time of day to limit differences in diurnal fluctuations.

8.6 Randomisation

Participants were randomised after baseline assessment. The participant chose from an equal number of opaque envelopes containing a piece of paper with either "intervention" or "control" written on it. Prior to each randomisation the envelopes were shuffled by the researcher. After randomisation the participant was given a regular timeslot for their training sessions and asked to return for their first training session after abstaining from exercise for at least two days.

They were instructed to make sure that they had eaten and drank something every morning before each training session.

8.7 Outcome measures

8.7.1 Primary outcome measure: feasibility of high intensity interval training

Feasibility was measured in terms of acceptability by tolerance to protocol, adherence in the percentage of training sessions completed, compliance rate with protocol, and the drop-out rate of participants (Bowen et al., 2009). A retention rate of 80% and compliance rate of 80% was considered to indicate an appropriate level of acceptability (Scottish Intercollegiate Guidelines Network, 2017).

Tolerance was measured by monitoring the participant's MS symptoms over a 48 hour period after each training session, and in the number of adverse events. Prior to each session the participant was given a symptom diary and asked to rate their pain, spasms, paraesthesia, fatigue and any other symptom they may have on a 10 point visual analogue scale (Appendix 12). After each training session the participant was asked to monitor the same symptoms on a visual analogue scale in the morning, afternoon and evening for 48 hours. In addition any changes to medication were also recorded in the diary. The diary was reviewed by the researcher and discussed with the participant at the next training session. If symptoms returned to baseline within the 48 hour time period, this was regarded as well tolerated. If symptoms had not returned to baseline after the 48 hour period this was discussed with the participant to see if the fluctuation in symptoms was a normal occurrence for them or not. If this was not normal for the participant and it repeatedly happened this was discussed with the participant, and the exercise protocol was adjusted for the next two sessions. If the exercise training was still producing an adverse effect on the participant's symptoms, withdrawal was considered.

8.8 Secondary outcome measures

8.8.1 Blood pressure and resting heart rate

During the exercise sessions, blood pressure and resting heart rate were measured using an Omron 7051T blood pressure and heart rate monitor. After the participant had been sitting for 10 minutes, two readings were taken 30 seconds apart and the mean of the readings was recorded. Readings were taken with the participant in a sitting position with their arm resting on a table with their palm facing up.

8.8.2 Timed 25 foot walk test

The participant was asked to walk 25 feet on a marked floor as quickly, but safely, as possible, using their usual walking aids or assistive devices. A stop watch was started when the participant began from a standing start and was stopped when they crossed the finish line. The test was repeated twice with no rest period between tests and the average of both times calculated. A maximum time of 180 seconds was placed on both trials as per the protocol set out by Cutter et al. (1999). If the participant did not manage the first trial in this time then they were not required to do the second trial.

The timed 25 foot walk test was found to be reliable in people in MS (Learmonth et al., 2012). Studies have found the timed 25 foot walk test correlated with the EDSS across all levels (Kalkers et al., 2000) but was less sensitive at lower levels of disability (Bethoux and Bennett, 2011). The Minimal Clinically Important Difference (MCID) for the timed 25 foot walk test in people with MS is a decrease of 20% in time (Kaufman et al., 2000).

8.8.3 Multiple Sclerosis Impact Scale - 29 version 2

The MSIS-29 version 2 self-report measure was described in Chapter 4 (section 4.9.3). The MSIS-29 is valid and sensitive to change in disability in people with

MS (Gray et al., 2009, McGuigan and Hutchinson, 2004). While the MCID for version 1 of the MSIS-29 is 8 points in the physical sub-scale (Costelloe et al., 2007a) and 6 in the psychological sub-scale (Widener and Allen, 2014) there is no available MCID for the sub-scales in MSIS-29 version 2. The MSIS-29 version 2 takes approximately 10 minutes to complete.

8.8.4 Hospital Anxiety and Depression Scale

The HADS is a self-report measure of depression and anxiety (Zigmond and Snaith, 1983). It consists of 14 items: 7 for depression and 7 for anxiety. The participant is asked to recall the past week and choose 1 of 4 possible options for each statement each scoring 0-3. Both depression and anxiety subscales are scored out of 21. A total score of 0-7 is considered normal, 8-10 borderline, and 11-21 indicates clinical symptoms and warrants further referral if the participant is not already receiving treatment (Zigmond and Snaith, 1983). The HADS has been found to be valid for identifying anxiety and depression in people with MS (Patten et al., 2015, Watson et al., 2014). The HADS takes approximately five minutes to complete.

8.8.5 Symbol Digit Modalities Test

The SDMT assesses mental processing speed by asking the participant to substitute as many numbers in a list of symbols in 90 seconds with the aid of a symbol key (Smith, 1982). There are two ways to administer the test: in a written or oral format (Benedict et al., 2008). The oral format was chosen as it was more suitable for people with MS due to potential deficits in fine motor control slowing down the participant's answer rate.

The participant was presented with a sheet containing a series of nine different symbols. At the top of the page was a key linking each of the symbols with the numbers one to nine (Appendix 13). The participant was asked to say the

corresponding number for each symbol of the series in order as quickly as they could in 90 seconds. The total number of correct answers was recorded.

The SDMT has been shown to be valid and reliable in detecting impaired mental processing speed in people in MS (Walker et al., 2016). The SDMT is also more valid than the paced auditory serial addition test, easier to administer (Drake et al., 2010) and is preferred by people with MS (Walker et al., 2012). A cut-off score of 40 or below indicates cognitive impairment, not just mental processing speed, in people with MS (Van Schependom et al., 2014). Changes in the SDMT are deemed to be likely to be clinically significant if they are of 8 or more and convincing if 12 or more (Benedict et al., 2012).

8.8.6 Fatigue Scale for Motor and Cognitive functions

The FSMC is a 20 item self-report measure which assesses the severity of fatigue on both motor and cognitive functions (Penner et al., 2009). Each question has the options 'Does not apply at all', 'Does not apply much', Slightly applies', 'Applies a lot' and 'Applies completely'. Each option scores 5, 4, 3, 2 and 1 respectively. The scores for all questions in each category are summed to give a score which can range from 10 to 50. The FSMC has defined cut-off scores to classify mildly, moderately and severely fatigued patients. Mild, moderate and severe cut off points are 22, 27 and 32 for the physical domain; 22, 28 and 34 for the cognitive domain; and 43, 53 and 63 for the total score (Penner et al., 2009). Both the motor and cognitive sub-scales have been shown to be valid in people with MS (Penner et al., 2009). The FSMC takes approximately 5 minutes to complete and the participant is asked to answer the questions in relation to their general day to day life.

8.8.7 Resting serum concentrations of brain derived neurotrophic factor

To test for BDNF, blood samples were collected before the HRMax test at the baseline assessment (week 0) and again at the post intervention assessment

(week 9). Blood was drawn into a serum vacutainer via venepuncture of the cubital fossa and left for 30 min to coagulate and then centrifuged at 3000 Revolutions Per Minute (RPM) for 20 minutes. When immediate centrifugation was not possible samples were stored at $\leq$ 5°C and for a maximum of 8 hours before centrifugation. Samples were then aliquoted and frozen at -80°C. Samples were thawed in batches and analysed using a Quantikine™ ELISA kit (R&D systems, catalogue number DBNT00).

8.8.8 Plasma concentrations of cholesterol, triglyceride and high density lipoprotein

To test for non-fasting triglycerides, and blood lipids, blood was drawn into an EDTA vacutainer and stored at $\leq$ 5°C. Plasma was separated with swing out centrifugation and frozen as described above (section 8.9.7). Samples were thawed in batches and concentrations of total cholesterol, triglyceride and High Density Lipoprotein (HDL) were obtained via Spectrophotometry using a Roche Cobas™ 311 Clinical Chemistry Analyser.

8.8.9 Whole blood lactate (resting and peak concentrations)

Whole blood lactate was measured using an Arkray™ Lactate Pro 2 handheld lactate analyser both before and after the HRMax test. A disposable pin prick lancet was used to obtain a droplet of blood (as low as 0.3 microlitres) from a sterilised forefinger or thumb pad of the participant. This droplet was drawn into a capillary sensor and test strip and after 5 seconds a concentration in mmol/l was provided. As per the ACSM definitions of maximal exertion, a post exercise reading of 8.0 mmol/l or above was considered to indicate maximal exertion (Thompson et al., 2000).

8.8.10 Maximal heart rate test

While the gold standard for measuring cardiovascular fitness is maximal oxygen consumption (VO_2 max), which gives a measure of ventilation of oxygen in ml/kg/min, the equipment for conducting VO_2 max testing was not available. Instead HRMax was selected as heart rate positively correlates with VO_2 consumption and the correlation becomes stronger as intensity rises (Gastinger et al., 2010). Uth et al. (2004) have shown that the HRMax and resting heart rate can be used to estimate VO_2 max with a strong correlation (r=0.87) using the following equation: VO_2max = 15 x (HRMax/ resting heart rate). The use of HRMax as a proxy measure for a work rate of $\%VO_2max$ is commonplace in exercise studies and was implemented in three of the six HIIT studies identified in the systematic review (Skjerbæk et al., 2014, Wens et al., 2015, Zimmer et al., 2017).

Maximal heart rate was measured using a graded exercise test on a Roger Black Gold™ cycle ergometer and a Polar™ heart rate monitor. Participants were asked, for the day of the test, to abstain from consuming caffeine prior to the test and to make sure that they had eaten before coming to the session. The ergometer seat height was adjusted accordingly to the ergonomics of the participant so that when the pedal was at its lowest point the participant's knee was flexed to approximately 25 degrees (Peveler et al., 2007). A Polar™ heart rate monitor chest sensor strap was moistened and attached to the participant's chest. The participant had a three minute warm up of unloaded pedalling at their own chosen cadence. The testing phase then began at resistance one (of eight) and a target speed of 30 km/h, which was an approximate cadence of 60 RPM. Resistance was then increased by one level every minute until resistance level eight was reached. The 10 point Borg Scale of Perceived Exertion was in front of the ergometer in view of the participant (described in section 8.9). The participant was given verbal encouragement throughout and asked to state their exertion from the 10 point Borg Scale of Perceived Exertion once a minute. If the participant was able to cycle at 30km/h at resistance level eight, the speed was increased by 5 km/h each minute thereafter. The researcher recorded the highest heart rate reached. Testing was stopped when one of the following occurred indicating volitional exhaustion:

- Unable to consistently sustain a cadence greater than 40 RPM
- Felt that they could not continue

At this point the warm down phase began where the participant pedalled at a nominal resistance and chosen low cadence for three minutes, or longer if the participant desired, or until their heart rate decreased to below 70% of the highest heart rate recorded.

The highest heart rate recorded was used to calculate training intensities for the HIIT and CONT sessions. The test generally lasted between 8-12 minutes. A fan was set up to keep the participant cool and two therapists were present for the entire test to the ensure safety of the participant and to help the participant on and off the cycle ergometer if required.

After the test the participant rested on a plinth for as long as needed but for a minimum of 10 minutes, as lower limb symptoms may be temporarily exacerbated by exercise. The participant was provided with water before and after the test to ensure they remained hydrated.

Maximal exertion during a cardiorespiratory test can be characterised by any one of the following (Midgley et al., 2007, Thompson et al., 2000):

- A perceived exertion of $\geq$18 on the Borg Scale of perceived exertion or $\geq$10 on the 10 point Borg Scale
- Heart rate plateau with increased workload
- Post-test lactate level > 8.0 mmol/l
- VO_2 consumption plateau with rising workload
- Respiratory exchange ratio of CO_2: O_2 of 1.10 or more

Due to the lack of available equipment, indicators of maximal exertion used were the criteria involving the Borg scale, a heart rate plateau and post-test lactate levels.

For safety reasons the HRMax test was also halted if any of the following occurred:

- Participant felt unwell

- Participant did not want to carry on
- Participant was unsteady/ felt dizzy or faint/ was sick/ became incoherent
- Participant was unable to control the exercise intensity and repeatedly exceeded target heart rate
- Participant had angina symptoms
- Participant displayed signs of poor perfusion: cyanosis, pallor, clammy or cold skin

8.9 10 point Borg scale of perceived exertion

The 10 point Borg scale of perceived exertion measures perceived physical exertion during physical activity. The scale ranges from '0 nothing at all' to '10 very, very strong (maximal)' (Appendix 14). The 10 point Borg scale of perceived exertion has been shown to be reliable and valid in people with MS and a mild to moderate disability whilst undertaking cycling exercise (Cleland et al., 2016). Furthermore, compared to the original Borg scale of rated perceived exertion which ranged from 6-20, the 10 point Borg scale was found to be more suitable for graded tests lasting more than four minutes (Borg and Kaijser, 2006).

8.10 Training protocols

The intervention and active control groups both received an eight week exercise programme. The participants attended the Douglas Grant Rehabilitation Centre in Ayrshire Central Hospital, Irvine, twice a week for supervised training sessions, with sessions separated by at least two days to allow for recovery. Participants received individual training sessions. A physiotherapist (the PhD student) was present for all training sessions. A Polar™ heart rate monitor chest sensor strap was moistened and attached to the participant's chest with the heart rate monitor placed on the handle bars so the participant could see their own heart rate. The seat height of the bicycle ergometer was adjusted in a similar way as the assessments (described above). A fan was set up to keep the participant cool. The 10 point Borg Scale of Perceived Exertion was placed in front of the cycle ergometer within the participant's view (Appendix 14). Safety

criteria for halting a training session were the same as those used for halting the HRMax test (8.8.10).

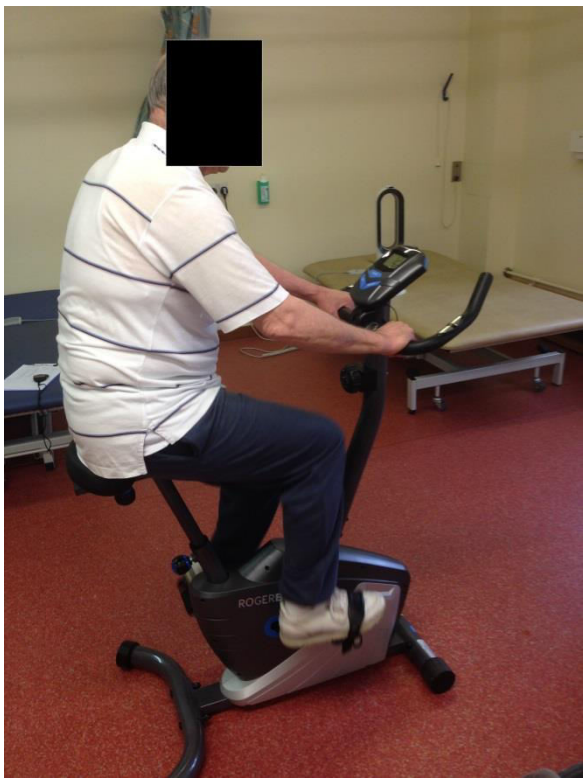

Figure 8-1 Participant position for exercise session

8.10.1 High intensity interval training protocol

The HIIT protocol consisted of a 2 minute warm up, 6 x 90 second bursts at 80-95% of HRMax with 90 second working rests in between, followed by a 3 minute warm down. The participant was informed of their 80-95% HRMax range and advised not to exceed this range during their exercise session. If the HRMax recorded during HRMax test was greater than the age predicted HRMax (220- age in years) then, for safety reasons, the range prescribed was 80-95% of age predicted HRMax.

The participant warmed up for 2 minutes by cycling at their self-selected light resistance and a cadence of ≤60 RPM to increase their heart rate to a minimum of 50% HRMax. If during the warm up the participant's heart rate did not increase to 50%, the resistance was increased manually by the researcher to

increase workload and thus heart rate. After the 2 minute warm up period the resistance of the ergometer was increased to 70% of maximal resistance recorded during HRMax test and the participant was asked to pedal at >60 RPM for 1.5 minutes to increase heart rate to 80-95% of HRMax. After the 1.5 minute training interval was complete the resistance was reduced to the participant's self-selected light resistance and the participant pedalled at ≤60 RPM for 1.5 minutes to bring their heart rate down to 60-70% HRMax. The 1.5 minute high intensity interval and 1.5 minute working rest were repeated another five times to give a total of six high intensity intervals and six working rest intervals. The participant then pedalled at <60 RPM with nominal resistance for three minutes as a warm down. Total time on the ergometer was 23 minutes and total working time at a high intensity was nine minutes per session.

Similar intensities were used in a previous HIIT study that equated 90% of HRMax to approximately 80% VO_2max and 70% of HRMax to approximately 65% VO_2max (Zimmer et al., 2017). Interval lengths of 1.5 minutes were selected as previous research has found that intervals of 2 minutes or shorter are more enjoyable (Cassidy et al., 2017). Even though the previous study to investigate HIIT in people with progressive MS used intervals of 3 minutes only 30-60 seconds of each interval was spent at a high intensity (Skjerbæk et al., 2014).

If the participant did not reach ≥80% HRMax in the first interval then for subsequent intervals the participant was encouraged to pedal faster and resistance was manually increased by the researcher. If the participant's heart rate exceeded 95% HRMax the participant was advised to decrease their RPM and the researcher manually decreased resistance. If during the first resting interval of the first training session the participant's heart rate did not decrease to less than 70% HRMax in 1.5 minutes, the resting interval was increased by 30 second increments up to 3.5 minutes and this increased duration was used for all following resting intervals for that session and sessions two to four. On the fifth session the resting interval was decreased by 30 seconds and then another 30 seconds every 4 sessions thereafter until it was 1.5 minutes.

The participant was given verbal encouragement and reassurance throughout. After the training session the participant was able to rest on a plinth for as long as needed as lower limb symptoms and fatigue may sometimes be temporarily

exacerbated. If the participant experienced pain, spasms, paraesthesia, fatigue or any other MS related symptom such as visual disturbances or dizziness these were recorded, the severity and the length of time for the symptoms to subside were also recorded and then monitored in subsequent sessions.

8.11 Active control protocol

The active control group received an eight week, CONT programme. The participants visited the Douglas Grant Rehabilitation Centre twice weekly for training sessions separated by at least two days to allow for recovery. Participants received individual supervised training sessions. An active control of CONT was used as the effectiveness of HIIT in producing increases in fitness has always been compared to CONT as this is the traditional endurance training method to improve fitness. Thus it was appropriate to compare these two training modalities in people with progressive MS.

8.11.1 Continuous moderate intensity session protocol

The participant was informed of their 60-70% HRMax range and told not to exceed this during the session. After a 2 minute warm up, cycling at a nominal resistance and $\leq$60 RPM the resistance was increased to 50% of maximal resistance recorded during the HRMax test and the participant cycled at ~60 RPM for 30 minutes, during which they were asked to keep their heart rate in the 60-70% HRMax range. If the participant exceeded 70% HRMax they were asked to decrease their RPM or the researcher manually decreased the resistance to decrease the workload. Conversely, if the participant did not reach 60% HRMax then they were asked to increase their RPM or the researcher manually increased the resistance to increase the workload. After the 30 minutes was complete the participant cycled for 3 minutes at a nominal resistance as a warm down. Total work time in the continuous moderate intensity training session was 30 minutes at 60-70% of HRMax. Participants in CONT group were also given the

opportunity to rest afterwards and any increase in the severity of symptoms and length of time to subside were recorded.

8.11.2 Comparison of the two training protocols

Energy cost of VO_2 is 20.5 kJ/l. Assuming a weight of 75kg, a VO_2 peak of 25.5 ml O_2/kg/min, and equating 70% HRMax to 60% VO_2Max (Langeskov-Christensen et al., 2015) this would equate to a consumption of 34.4 l O_2 per CONT session, or 705.2 kJ. A similar calculation for the HIIT protocol, assuming 90% HRMax equates to 80% VO_2max, totals at 13.8 l O_2, or 282.9 kJ. Despite this difference in workload with the HIIT group apparently burning less energy during training, previous research, using similar protocols in healthy individuals, has shown that due to Excess Post-exercise Oxygen Consumption, the total energy expenditure or VO_2 consumed both in working intervals, rests during the HIIT session and afterwards, is similar or greater that the CONT session (Tremblay et al., 1994, Gaesser and Brooks, 1984). A comparison of the two training protocols can be seen in Figure 8-2.

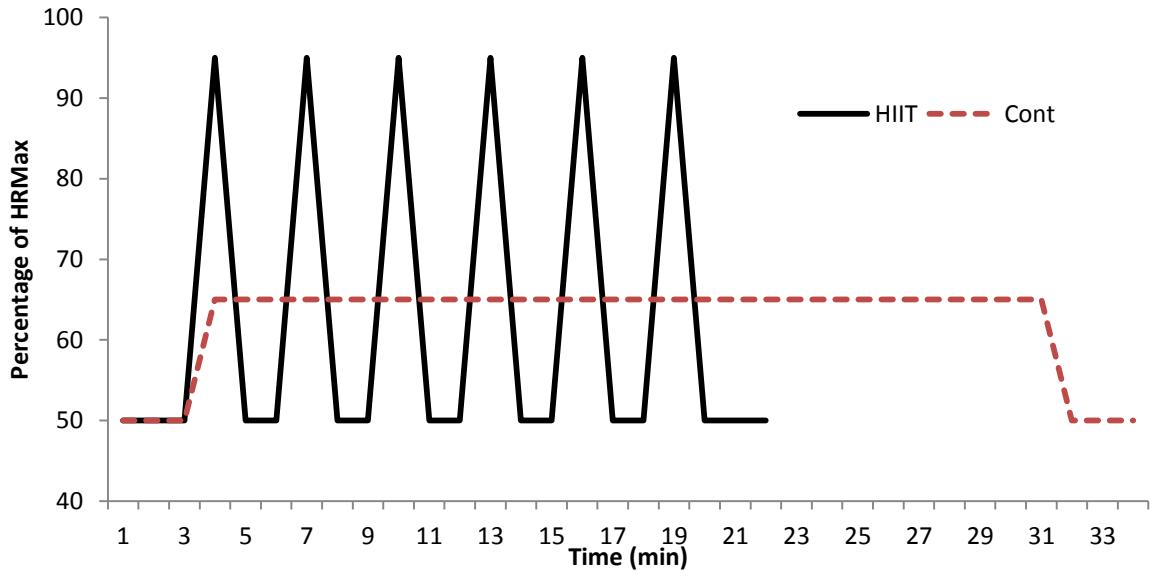

Figure 8-2 Exercise intensity for high intensity interval training and continuous training sessions

Abbreviations: HIIT: high intensity interval training; CONT: continuous moderate intensity interval training; HRMax: maximal heart rate

8.12 Statistical analysis and handling of data

All data analysis was conducted using IBM SPSS Statistics version 22. Continuous variables were assessed for normality using Kolmogorov-Smirnov tests and means with standard deviations (SD), or medians with ranges, were reported as appropriate. Baseline continuous variables were compared between training groups using independent sample t tests, or Mann Whitney U tests when the data were not normally distributed. Categorical variables were compared using chi square tests.

The difference between pre and post intervention measures was calculated for each participant and the means of these differences were compared between the two training groups using independent sample t tests and Mann Whitney U tests where appropriate. Effect sizes of all statistically significant results were calculated using Cohen's *d* analysis. Effect sizes were defined as weak ($d<0.5$), moderate ($0.5\leq d<0.8$) or strong ($d\geq 0.8$) (Cohen, 1988). Statistical significance was set at $p<0.05$ and all analysis was conducted per protocol.

Adherence was calculated as a percentage of sessions attended and compliance was calculated as the percentage of training sessions where protocol was followed successfully.

8.13 Participants

Twenty four people with progressive MS expressed an interest in taking part in the study. Twelve were excluded for the following reasons: non progressive MS (n=3), failed to respond to telephone messages after expressing an interest (n=2), EDSS<4.0 (n=1), myocardial infarction less than a year ago and was taking a beta blocker (n=1), taking a beta blocker (n=1), uncontrolled high blood pressure at screening (n=1), chronic obstructive pulmonary disorder (n=1), participating in another intervention study for their MS (n=1) and unable to commit to the timeframe (n=1).

Twelve people were then included in the study, underwent screening and baseline measurements, before being randomised. One participant withdrew

from the HIIT group due to new personal time constraints and one participant withdrew from the CONT group because they did not enjoy cycling. See Figure 8-3 for a CONSORT diagram describing the flow of participants through the study.

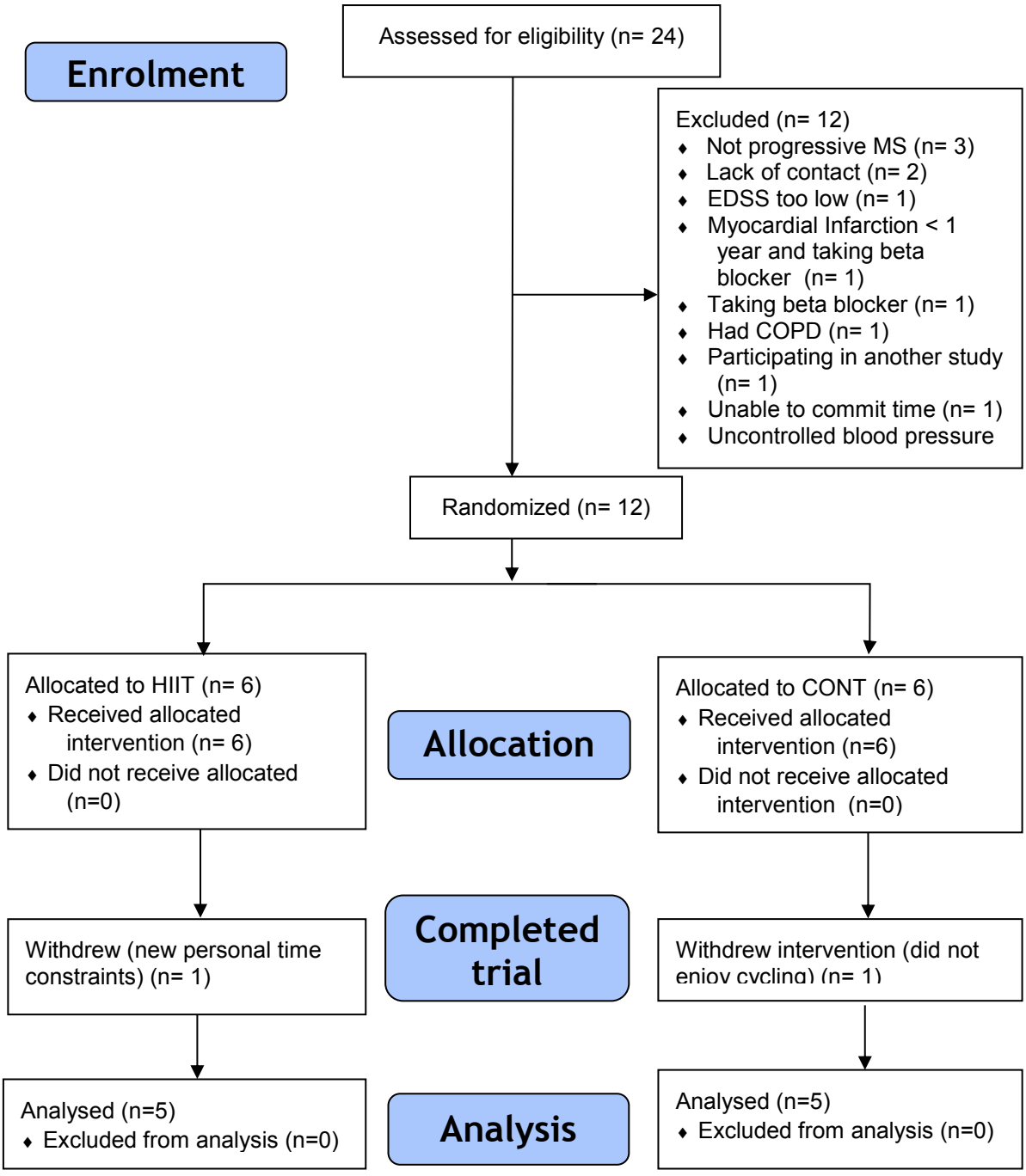

Figure 8-3 CONSORT diagram of flow of participants through the study

Abbreviations: n: number; EDSS: extended disability status scale; COPD: chronic obstructive pulmonary disorder; HIIT: high intensity interval training; CONT: continuous moderate intensity interval training

8.14 Restarting of five participants

During the study period the PhD student became ill and was unable to carry out the intervention for four weeks. At that point, six participants (participants 7-12) were still receiving the intervention and six had already completed their final assessment. Of the six participants who were still receiving the intervention, two were in the CONT group and four were in the HIIT group. As the intervention was eight weeks in length the decision was taken to restart these participants, collect new baseline data and start a new eight week training programme. It was at this point one of the participants (number 12) decided to withdraw as he did not enjoy cycling. For participants 7-11, the baseline data reported in this chapter is the second set of measurements collected. For these five participants statistical analysis revealed no difference between the two sets of baseline measurements (p>0.05). A comparison of the two sets of baseline data can be seen in Appendix 15.

8.15 Demographics

The cohort comprised eight males and four females, eight had SPMS and four had PPMS. The mean age was 54 years (SD 8) and mean time since diagnosis was 15 years (SD 12). The median EDSS score was 6.0 (range 4.0–6.0) (Table 8-1). One participant used an ankle foot orthosis and one participant used functional electrical stimulation (Table 8-2). The mean Body Mass Index (BMI) across the sample was 26.4 (SD 3.2) kg/m^2 (Table 8-1). Three participants were a healthy weight (BMI <25 kg/m^2), six were overweight (BMI 25-30 kg/m^2) and three participants were obese (BMI >30 kg/m^2) (NICE, 2014c) (Table 8-2). Only one participant was working full time and one part time, all the other participants were either retired, or unemployed (Table 8-2).

Table 8-1 Demographics of the cohort

	Whole sample		HIIT		CONT		
	Mean	SD	Mean	SD	Mean	SD	*P*
Age (years)	54	8	54	8	54	9	0.973
TSD (years)	15	12	13	11	18	12	0.463
Height (m)	1.72	0.15	1.72	0.16	1.72	0.14	0.982
Weight (kg)	80.2	10.2	82.7	14.3	77.8	3.2	0.443
BMI (kg/m^2)	26.4	3.2	27.4	2.9	25.9	3.3	0.489
EDSS*	6.0	4.5-6.0	6.0	4.0-6.0	6.0	4.0-6.0	0.574^
Gender: Male	8		4		4		
(n) Female	4		2		2		
MS type†: PPMS	4		3		1		
(n) SPMS	8		3		5		

Abbreviations: TSD: time since diagnosis, BMI: body mass index; EDSS: expanded disability status scale; PPMS: primary progressive MS; SPMS: secondary progressive MS HIIT: high intensity interval training: CONT: continuous moderate intensity training SD: standard deviation
*EDSS expressed as median and range
^All tests compared HIIT and CONT groups and were independent samples t tests, apart from EDSS which was Chi-Square test

There was an equal distribution of males and females across the HIIT and CONT groups with four males and two females in each. There were three people with PPMS and three people with SPMS in the HIIT group and five people with SPMS and one person with PPMS in the CONT group (Table 8-1). There were no differences between the two groups in terms of age, time since diagnosis, height, weight or EDSS (Table 8-1).

Table 8-2 Demographics of participants

Pt	Group	Age (yrs)	Gender	MS Type	TSD	TSR	Indoor WA	Outdoor WA	WC Use	Working	Height (m)	Weight (kg)	BMI (kg/m^2)	EDSS
1	HIIT	45	M	SPMS	12	>2 yrs	1 ws	1 ws	weekly	Ret	1.82	89.7	27.1	6
2	HIIT	57	F	SPMS	30	1-2 yrs	1 ws	1 ws	occ	UE	1.53	75.3	32.2	6
3	CONT	52	F	SPMS	5	>2 yrs	1 ws	1 ws	occ	Ret	1.57	73.6	29.9	6
4	CONT	46	M	SPMS	8	>2 yrs	none	none	never	Ret	1.78	75.6	23.9	4
5	CONT	65	M	SPMS	29	unknown	1 ws	1 ws	never	Ret	1.91	82	22.5	6
6	CONT	43	M	PPMS	11	none	1 ws	1 ws	occ	FT	1.75	77.2	25.2	6
7	HIIT	64	M	PPMS	20	none	1 ws	1 ws	never	Ret	1.74	79.5	26.3	6
8	HIIT	49	M	PPMS	1	none	none	none	never	Ret	1.78	97	30.7	4.5
9	HIIT	62	M	PPMS	10	none	1 ws	1 ws	never	Ret	1.91	95.2	26.1	6
10	CONT	62	F	SPMS	36	3/12-1 yr	1 ws	1 ws	occ	UE	1.55	77.1	32.1	6
11	HIIT	49	F	SPMS	2	3/12-1 yr	none	none	never	PT	1.52	59.4	25.7	4
12	CONT	57	M	SPMS	17	1-2 yrs	none	1 ws	occ	Ret	1.75	81	26.4	6

Abbreviations: Pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; M; male; F: female; SPMS: secondary progressive MS; PPMS: primary progressive MS; TSD: time since diagnosis; TSR: time since last relapse; 3/12: 3 months; yrs: years; WA: walking aid; ws: walking stick; AFO: ankle foot orthosis; FES: functional electrical stimulation; WC: wheelchair; occ: occasional; Ret: retired; UE: unemployed; FT: full time; PT: part time; BMI: body mass index; EDSS: expanded disability status scale

8.16 Baseline data

8.16.1 Cardiovascular related outcome measures

As a cohort the participants had a HRMax lower than that of their age predicted HRMax, suggesting they were deconditioned. The mean age was 54 years and thus the mean age predicted HRMax was 166 bpm (220-54) (Table 8-3).

Table 8-3 Baseline measurements of cardiovascular related outcome measures for each participant

Pt	Group	Weight (kg)	Resting HR (bpm)	Systolic (mm/Hg)	Diastolic (mm/Hg)	HRMax (bpm)
3	CONT	73.6	87	144	77	174
4	CONT	75.6	69	120	70	180
5	CONT	82	73	117	72	136
6	CONT	77.2	72	126	84	170
10	CONT	77.1	93	125	76	124
12	CONT	81	83	129	85	116
1	HIIT	89.7	70	126	78	137
2	HIIT	75.3	63	142	74	110
7	HIIT	79.5	66	108	64	135
8	HIIT	97	59	123	80	137
9	HIIT	95.2	82	128	97	138
11	HIIT	59.4	75	126	74	137
All	**Mean**	**80.2**	**74**	**126**	**78**	**141**
	SD	**10.2**	**10**	**10**	**8**	**22**
CONT	**Mean**	**77.8**	**80**	**127**	**77**	**150**
	SD	**3.2**	**1**	**10**	**6**	**28**
HIIT	**Mean**	**82.7**	**69**	**126**	**78**	**132**
	SD	**14.3**	**8**	**11**	**22**	**11**
	P	**0.443***	**0.075***	**0.825***	**0.924***	**0.519^**

Abbreviations: Pt: participant number; CONT: continuous moderate intensity training; HIIT: high intensity interval training; SD: standard deviation; HR: heart rate; HRMax: maximal heart rate
*Result from independent t test between HIIT and CONT groups.
^Result from Mann Whitney U test between HIIT and CONT groups.

The mean HRMax of the sample was 141 (SD 22) bpm. This indicated that as a cohort their HRMax was approximately that of a 79 year old. The cohort had a healthy resting HR of 74 (SD 10) bpm but the large standard deviation reflected that four participants had a high resting HR of 80 bpm or above (Table 8-3). Diastolic and systolic blood pressures were in normal ranges across the whole cohort. This was expected as uncontrolled high blood pressure was an exclusion criterion. There were no differences between the groups at baseline in terms of weight (p=0.443), resting HR (p=0.075), systolic (p=0.825) or diastolic blood pressure (p=0.924), or HRMax (p=0.519) (Table 8-3).

8.16.2 Multiple Sclerosis clinical outcome measures

Mean time to complete the timed 25 foot walk test was 10.9 (SD 7.9) seconds (Table 8-4). The large standard deviation highlights the large range of results across the 12 participants (5.2 – 23.5 seconds). Participants with the slowest times had an EDSS of 6.0 and used a walking stick both indoors and outdoors. Results from the HADS suggested that the cohort were not anxious or depressed with mean scores of 7 (SD 3.9) and 6 (SD 3.2) respectively (Table 8-4). However, one participant had a depression score of 11, and three participants had anxiety scores of 11 or more indicating potential high levels of depression and anxiety. As a cohort the mean physical impact score from the MSIS-29 was 53 (SD 13.8) from a maximal score of 80, indicating a moderate amount of physical impact. The mean psychological impact score from the MSIS-29 was 22 (SD 8) from a maximal score of 36 also indicating a moderate psychological impact of MS.

Table 8-4 Baseline measurements of gait speed, impact of disease and anxiety and depression scores for each participant

Pt	Group	T25FW (sec)	MSIS29 Phys	MSIS29 Psych	HADS Anx	HADS Dep
3	CONT	18.1	68	23	15	11
4	CONT	5.4	48	19	7	7
5	CONT	5.2	36	15	2	7
6	CONT	10.2	31	11	6	2
10	CONT	23.5	51	34	3	5
12	CONT	11.9	76	36	9	9
1	HIIT	6.8	55	21	7	4
2	HIIT	22.7	74	27	11	8
7	HIIT	8.7	53	17	6	5
8	HIIT	5.3	50	19	8	0
9	HIIT	7	48	11	3	5
11	HIIT	6.2	45	25	12	10
All	**Mean**	**10.9**	**53**	**22**	**7**	**6**
	SD	**7.9**	**14**	**8**	**4**	**3**
CONT	**Mean**	**12.4**	**52**	**23**	**7**	**7**
	SD	**7.2**	**18**	**10**	**5**	**3**
HIIT	**Mean**	**9.5**	**54**	**20**	**8**	**5**
	SD	**6.6**	**10**	**6**	**3**	**3**
	p	**0.522^**	**0.770***	**0.543***	**0.730***	**0.448***

Abbreviations: Pt: participant number; CONT: continuous moderate intensity training; HIIT: high intensity interval training; SD: standard deviation; T25FW: timed 25 foot walk test; MSIS-29: multiple sclerosis impact scale; Phys: physical sub-scale; Psych: psychological sub-scale; HADS: hospital anxiety and depression scale; Anx: anxiety; Dep: depression
*Result from independent t test between HIIT and CONT groups.
^Result from Mann Whitney test between HIIT and CONT groups.

The mean fatigue score measured by the total score from the FSMC, for all participants was 73 (SD 22.4) indicating that the cohort as a whole was severely fatigued (cut off score of 63, n=8). Mean scores of 38 (SD 9.8) for motor fatigue also meant that the sample was severely fatigued in this domain (cut off 34, n=8) and a mean score of 35 (SD 12.7) indicated the same for the domain of cognitive fatigue (cut off 32, n=8) (Penner et al., 2009) (Table 8-5).

Table 8-5 Baseline measurements of fatigue and mental processing speed for each participant

Pt	Group	FSMC Total	FSMC Mot	FSMC Cog	SDMT
3	CONT	100	50	50	47
4	CONT	70	37	33	46
5	CONT	42	25	17	30
6	CONT	34	23	11	57
10	CONT	92	48	44	15
12	CONT	100	50	50	15
1	HIIT	74	36	38	57
2	HIIT	88	44	44	33
7	HIIT	87	45	42	34
8	HIIT	83	42	41	28
9	HIIT	50	26	24	43
11	HIIT	61	33	28	48
All	**Mean**	**73**	**38**	**35**	**38**
	SD	**22**	**10**	**13**	**14**
CONT	**Mean**	**73**	**39**	**34**	**35**
	SD	**30**	**12**	**17**	**18**
HIIT	**Mean**	**74**	**38**	**36**	**41**
	SD	**15**	**7**	**8**	**11**
	p	**0.952***	**0.848***	**0.800***	**0.532***

Abbreviations: Pt: participant number; CONT: continuous moderate intensity training; HIIT: high intensity interval training; SD: standard deviation; FSMC: fatigue scale for motor and cognitive function; Mot: motor; Cog: cognitive; SDMT: symbol digit modalities test
*Result from independent t test between HIIT and CONT groups.

When metal processing speed was measured using the SDMT, the scores across the cohort ranged from 15 to 57 with a mean of 38 (SD 14.3). A score below 40 indicates cognitive impairment in people with MS (Van Schependom et al., 2014), indicating that this cohort as a whole had impaired mental processing speed. However, six of the twelve participants had scores over 40 meaning only half of the participants were cognitively impaired (Table 8-5).

There were no differences between the HIIT and CONT groups at baseline in the timed 25 foot walk test (p=0.522), MSIS-29 physical (p=0.77) and psychological sub-scale scores (p=0.543), HADS anxiety (p=0.73) or depression scores (p=0.448) (Table 8-4), SDMT scores (p=0.532), total FSMC scores (p=0.952), motor FSMC scores (p=0.848), or cognitive FSMC scores (p=0.800) (Table 8-5).

8.16.3 Physiological outcomes

Non-fasting levels of triglyceride across the whole cohort, were low with a mean concentration of 1.8 (SD 0.9) mmol/l, indicating healthy levels of circulating triglyceride with only three participants displaying non-fasting triglyceride levels over the healthy limit of 2.3 mmol/l. Total cholesterol concentrations were slightly above the healthy range (5.0 mmol/l), with a mean concentration of 5.8 (SD 0.9) mmol/l. Two participants, had total cholesterol levels over 7.0 mmol/l, indicating that while they would warrant an intervention to lower their cholesterol, their levels were not high enough to warrant further investigation (>7.5 mmol/l) (NICE, 2014a) (Table 8-6). However, none of the participants were taking a statin or similar cholesterol lowering medication.

Concentrations of HDL varied across the cohort with a mean concentration of 1.3 (SD 0.4) mmol/l indicating, as a cohort, they were on the limit of the healthy range (1.0 mmol/l). Three participants had HDL concentrations below 1.0 mmol/l and two of these had high levels of non-HDL cholesterol.

The mean BDNF concentration for this sample was 36.40 (SD 7.8) ng/ml indicating that baseline serum BDNF concentrations were within the average expected range of 8-46 ng/ml for healthy individuals (Polacchini et al., 2015) (Table 8-6).

Table 8-6 Baseline physiological measurements for each participant

Pt	Group	TG	Total chol	HDL	Non HDL chol	Resting lactate	Peak lactate	BDNF
3	CONT	1.5	7.2	0.9	6.2	5.6	7.8	50.18
4	CONT	1.5	4.7	1.6	3.1	4.5	18.5	31.74
5	CONT	1.5	5.2	1.5	3.7	4.8	6	37.99
6	CONT	3.5	5.9	0.8	5.1	2.1	8.1	36.12
10	CONT	2.9	5.9	1.1	4.8	2.5	4.3	33.33
12	CONT	1.3	6.2	1.3	4.9	2.1	3.8	40.83
1	HIIT	0.9	5.1	1.8	3.3	0.6	6.2	19.60
2	HIIT	0.6	5.1	1.9	3.2	0.8	4.6	41.03
7	HIIT	2.3	6.8	1.3	5.6	5.4	11.6	36.14
8	HIIT	1.6	4.5	0.9	3.6	1	15.5	34.81
9	HIIT	1.4	7.0	1.6	5.4	1.5	12.4	44.91
11	HIIT	2.5	5.7	1.2	4.5	1.7	4.4	29.68
All	**Mean**	**1.8**	**5.8**	**1.3**	**4.7**	**2.7**	**8.6**	**36.36**
	SD	**0.9**	**0.9**	**0.4**	**1.1**	**1.8**	**4.8**	**7.79**
CONT	**Mean**	**2.0**	**5.8**	**1.2**	**4.6**	**3.6**	**8.1**	**38.40**
	SD	**0.9**	**0.8**	**0.3**	**1.2**	**1.6**	**5.4**	**6.60**
HIIT	**Mean**	**1.5**	**5.7**	**1.5**	**4.2**	**1.8**	**9.1**	**34.34**
	SD	**0.8**	**1.0**	**0.4**	**1.2**	**1.8**	**4.7**	**8.90**
	p	**0.350***	**0.801***	**0.225***	**0.527***	**0.037^**	**0.730***	**0.399***

Abbreviations: pt: participant number; CONT: continuous moderate intensity training; HIIT: high intensity interval training; SD: standard deviation; TG: triglyceride; chol: cholesterol; HDL: high density lipoprotein; BDNF: brain derived neurotrophic factor
*Result from independent t test between HIIT and CONT groups.
^Result from Mann Whitney test between HIIT and CONT groups.
All values are in mmol/l apart from BDNF concentrations which are ng/ml.

Peak lactate at baseline assessment across the whole cohort was 8.6 (SD 4.84) mmol/l indicating, according the 8.0 mmol/l cut-off (Thompson et al., 2000, Midgley et al., 2007), that they reached maximal exertion during their exercise test (Table 8-6). However, only five of the 12 participants were above the cut-off of 8.0 mmol/l and one participant (participant 4), who was an ex-naval serviceman and previously experienced in maximal exertion testing, produced a peak lactate of 18.5 mmol/l (Table 8-6). The two participants with the highest

peak lactate at baseline also had the lowest EDSS scores of 4.0 and 4.5 (Table 8-2).

There were no differences between the groups at baseline in terms concentrations of triglyceride (p=0.35), total cholesterol (p=0.801), HDL (p=0.225), non-HDL cholesterol (p=0.527) BDNF (p=0.399) or peak lactate (p=0.73). There was a statistically significant difference between the HIIT and CONT groups in resting lactate (p=0.037). The CONT group had a higher resting lactate; mean of 3.6 mmol/l compared to 1.8 mmol/l in the HIIT group (Table 8-6).

8.17 Post intervention results: primary outcome measure of feasibility

8.17.1 Adherence and drop-out rate

Adherence in both groups was equally high with 98.8% attendance at exercise sessions. All participants apart from two, one in each group, attended all their training sessions. One participant dropped out from each group. The participant who dropped out of the HIIT group did so because of new personal time constraints which meant that she was unable to continue attending. The participant who dropped out of the CONT group did so because he did not enjoy cycling. The baseline data for these participants was included in the statistical analysis comparing the HIIT and CONT groups at baseline and is presented for each outcome for comparison. The subsequent analysis was conducted on a per protocol basis.

8.17.2 Tolerance

Both the HIIT and CONT protocols were well tolerated. No participants reported any fluctuation in their MS symptoms, that could be attributed to the intervention, and that did not return to baseline within the 48 hour monitoring period.

There were no adverse events in the HIIT group. There were, however, three adverse events in the CONT group. One participant (participant 5) stopped two of his training sessions prematurely complaining of a headache and dizziness. He later informed the PhD student that on both occasions that he had not been feeling well prior to the training session and had not eaten or drunk anything on either morning. He was advised on both occasions that he should be hydrated and eat before exercising. Another participant (participant 10) stopped one of her training sessions due to pain in her right knee while cycling. The pain resolved immediately after stopping the session and after adjusting the height of the seat at subsequent sessions she did not experience any further pain. Up until this point the participant's seat had been, at the participant's request, lower than described in the protocol.

8.17.3 Compliance with protocol

The compliance rate with the whole protocol was 89.6%. From a total of 164 sessions, across both groups, two were stopped early due to participant 5 not feeling well and one was stopped early due to participant 10 experiencing knee pain while cycling. Furthermore, for all of her 15 training sessions, participant 10 trained at a percentage of her HRMax which was higher than her protocol due to her deconditioned baseline measurements (discussed in more detail in section 8.18). This therefore equated to a total of 17 sessions where the protocol was not complied with. However all instances of non-compliance were in the CONT group meaning compliance rate with the CONT protocol was 79.3% and compliance with the HIIT protocol was 100%.

The contingency plan described in the HIIT protocol to increase the length of working rest intervals if a participant's heart rate did not drop back down to below 70% of the HRMax during their working rest (section 8.10.1) was never implemented as it was not necessary.

8.18 Results from one participant

Participant 10 had an exercise profile different to the other participants in the study. In the participant's baseline exercise test she reached a maximal resistance of 2, was on the exercise bike for 4 minutes 38 seconds before starting the warm down, and reached a HRMax of 124 bpm. After randomisation she was allocated to the CONT group, however due to such a low HRMax, when she trained at nominal resistance, her heart rate was always above 70% of her HRMax. In her initial training session she was able to cycle for 9 min 37 seconds before having to stop due to being fatigued. Over the next seven sessions her time on the cycle ergometer steadily progressed, apart from one session where she had to stop due to knee pain, so that on her eighth session she was able to cycle for the full 30 minutes. For the rest of the sessions she managed the full 30 minutes (with warm up and cool down). Her working heart rate was calculated by noting her heart rate every five minutes and taking an average. This working heart rate dropped from 88% of her HRMax in her first training session to 78% in her final session, indicating an improvement in working heart rate and thus fitness (Table 8-7). This meant that the participant's average working heart rate was 85% HRMax. This was higher that the training zone of 60-70% of HRMax prescribed by the protocol for the CONT group. It should be noted that throughout all the training sessions the resistance was on the lowest level and the workload was never increased as her HRMax was never within, or below, her training zone of 60-70% of HRMax.

When the participant completed her post intervention HRMax test she reached a maximal resistance of 5, was on the exercise bike for 7 minutes 16 seconds before starting the warm down, but only reached a HRMax of 105 bpm with a peak lactate that was 0.4 mmol/l lower than her baseline measurement. This HRMax value, which was lower than baseline and previous working heart rates during training, was an unexpected result and was treated as an outlier. Due to this participant being an outlier, and the fact that the participant trained at a continuous steady state of 85% HRMax, statistical tests were run both including and excluding this participant's data.

Table 8-7 Participant 10's progression of working heart rate and length of session over the 16 training sessions

Training session number	HR average (bpm)	% HRMax	Time (min)
1	110	89	8.37
2	112	90	13.06
3	110	89	18.03
4	113	91	20.01
5	113	91	26.35
6	110	89	28.00
7	106	85	12.29*
8	109	88	30.00
9	107	86	30.00
10	101	81	30.00
11	106	85	30.00
12^	-	-	-
13	98	79	30.00
14	97	78	30.00
15	98	79	30.00
16	97	78	30.00

Abbreviations: HR: heart rate; HRMax: maximal heart rate
*Session stopped early due to knee pain.
^The participant missed session 12 due to transport issues.

8.19 Post intervention results: trends in secondary outcome measures

8.19.1 Cardiovascular related outcome measures

In the HIIT group all participants improved their HRMax (range 12-19 bpm). In the CONT group three participants improved (range 2-5 bpm) and two participants decreased their HRMax by 8 and 19 bpm (Table 8-8). These trends were confirmed as the mean differences between the two groups was statistically significantly different post intervention (p=0.013). This may indicate that HIIT had a positive effect on HRMax while CONT did not have an effect.

There was no trend displayed in resting HR in either the HIIT or the CONT group and there were no difference between the changes in either group. This may indicate that neither HIIT nor CONT had an effect on resting HR (*p*=0.605) (Table 8-8).

Table 8-8 Baseline, post-trial and difference between the measurements of resting heart rate, and maximal heart rate for each participant

		Rest HR (bpm)			HRMax (bpm)		
Pt	Group	Base	Post	Diff	Base	Post	Diff
1	HIIT	70	74	4	137	156	19
2	HIIT	63	60	-3	110	126	16
7	HIIT	66	62	-4	135	150	15
8	HIIT	59	67	8	137	149	12
9	HIIT	82	67	-15	138	154	16
11*	HIIT	75			137		
	Mean	69	66	-2	132	147	16
	SD	8	5	9	11	12	3
3	CONT	87	65	-22	174	178	4
4	CONT	69	67	-2	180	182	2
5	CONT	73	75	2	136	124	-8
6	CONT	72	74	2	170	175	5
10	CONT	93	87	-6	124	105	-19
12*	CONT	83			116		
	Mean	80	74	-5	150	153	-3
	SD	10	9	10	28	36	10
	p			0.605			0.013

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; SD: standard deviation; base: baseline; post: post intervention; diff: difference between baseline and post-trial; HRMax: maximal heart rate
*No post intervention measurements for participants 11 or 12 as both dropped out.

In the HIIT group there was a trend towards an increase in systolic blood pressure as four of the participants displayed an increase (range -2 – 30 mmHg) while there was no notable trend in the changes of systolic blood pressure in the CONT group. There was, however, no difference between the changes of the two groups (*p*=0.089) (Table 8-9).

There were no noticeable trends in changes of diastolic blood pressure in either training group and there was no difference between the changes of the two training groups (p=0.649) (Table 8-9). These results may suggest that neither HIIT nor CONT had an effect on blood pressure levels.

Table 8-9 Baseline, post-trial and difference between the measurements of blood pressure rate for each participant

		Rest systolic (mm/Hg)			Rest Diastolic (mm/Hg)		
Pt	Group	Base	Post	Diff	Base	Post	Diff
1	HIIT	126	132	6	78	72	-6
2	HIIT	142	140	-2	74	72	-2
7	HIIT	108	138	30	64	72	8
8	HIIT	123	152	29	80	90	10
9	HIIT	128	154	26	97	106	9
11*	HIIT	126			74		
	Mean	126	143	18	78	82	4
	SD	11	9	15	11	15	7
3	CONT	144	157	13	77	91	14
4	CONT	120	115	-5	70	71	1
5	CONT	117	124	7	72	73	1
6	CONT	126	130	4	84	81	-3
10	CONT	125	119	-6	76	71	-5
12*	CONT	129			85		
	Mean	127	129	3	77	77	2
	SD	9	17	8	6	9	7
	p			0.089			0.649

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; SD: standard deviation; base: baseline; post: post intervention; diff: difference between baseline and post-trial; HRMax: maximal heart rate
*No post intervention measurements for participants 11 or 12 as both dropped out.

8.19.2 Multiple Sclerosis clinical outcome measures

There was no trend in changes in timed 25 foot walk test in either training group and there was no difference between the changes of the groups (p=1.000) (Table 8-10). There were however, two participants who improved more than the 20% MCID for people with MS (Kaufman et al., 2000). One of these was in the CONT

group (participant 6: 20%) and one in the HIIT group (participant 2: 38%). Both of these participants reported that subjectively the intervention had a large positive impact on them.

Table 8-10 Baseline, post-trial and difference between the measurements of the timed 25 foot walk test for each participant

		T25FWT (sec)		
Pt	Group	Base	Post	Diff
1	HIIT	6.8	6.3	-0.5
2	HIIT	22.7	14.1	-8.6
7	HIIT	8.7	9.0	0.3
8	HIIT	5.3	6.4	0.9
9	HIIT	7.0	6.2	-0.8
11*	HIIT	6.2		
	Mean	9.5	8.4	-1.7
	SD	6.6	3.4	3.9
3	CONT	18.1	14.9	-3.2
4	CONT	5.4	5.1	-0.3
5	CONT	5.2	5.5	0.3
6	CONT	10.2	8.2	-2.0
10	CONT	23.5	23.9	0.4
12*	CONT	11.9		
	Mean	12.4	11.5	-1.0
	SD	7.2	8.0	1.6
	p			1.000

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; T25FW: timed 25 foot walk test; base: baseline; post: post –trial; diff: difference between baseline and post-trial
*No post intervention measurements for participants 11 or 12 as both dropped out.

In the HIIT group there were no noticeable trends in total fatigue, motor fatigue or cognitive fatigue when measured by the FSMC, and this was also the case for the CONT group. There was also no difference between the two training groups in changes in total fatigue (p=0.621), motor fatigue (p=0.695), or cognitive fatigue scores (p=0.474) (Table 8-11). One participant (participant 3) reported a large decrease in their overall score, of 25 points, and (decreases of 13 and 12

points in the motor and cognitive scores respectively). However, despite the large decrease this patient remained in the severely fatigued category (cut-off of 63), as her baseline score was 100/100 (Table 8-11). Subjectively, the intervention had a profound effect on this participant. At the beginning she reported fatigue to be her most disabling symptom, commenting while completing the FSMC, "I feel like this is describing me". Prior to the study, she was a non-exerciser and reported that at least once a week she would be bedridden by fatigue for an entire day. After starting the intervention, this happened just once, in the first week, after a long day of travelling.

Table 8-11 Baseline, post-trial and difference between the measurements of the total, motor and cognitive scores of the fatigue scale of motor and cognitive function for each participant

		FSMC total			FSMC motor			FSMC Cognitive		
Pt	Group	Base	Post	Diff	Base	Post	Diff	Base	Post	Diff
1	HIIT	74	74	0	36	37	1	38	37	-1
2	HIIT	88	94	6	44	45	1	44	49	5
7	HIIT	87	83	-4	45	40	-5	42	43	1
8	HIIT	83	82	-1	42	39	-3	41	43	2
9	HIIT	50	33	-17	26	20	-6	24	13	-9
11*	HIIT	61			33			28		
	Mean	74	72	-3	38	36	-2	36	37	0
	SD	15	23	9	7	10	3	8	14	5
3	CONT	100	75	-25	50	37	-13	50	38	-12
4	CONT	70	54	-16	37	28	-9	33	25	-8
5	CONT	42	48	6	25	28	3	17	20	3
6	CONT	34	35	1	23	23	0	11	12	1
10	CONT	92	92	0	48	48	0	44	44	0
12*	CONT	100			50			50		
	Mean	73	61	-7	39	33	-4	34	28	-3
	SD	29	23	13	12	10	7	17	13	6
	p			0.621			0.695			0.474

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; FSMC: fatigue scale of motor and cognitive function; base: baseline; post: post –trial; diff: difference between baseline and post-trial
*No post intervention measurements for participants 11 or 12 as both dropped out.

In the HIIT group four of the participants decreased their MSIS-29 physical sub-scale score and one remained the same (range -7 - 0). There was no trend in changes in the CONT group in this variable. However, there was no difference between the changes of the two training groups (p=0.845) (Table 8-12).

Table 8-12 Baseline, post-trial and difference between the measurements of the physical and psychological sub-scales of the multiple sclerosis impact scale for each participant

		Physical			Psychological		
Pt	Group	Base	Post	Diff	Base	Post	Diff
1	HIIT	55	49	-6	21	15	-4
2	HIIT	74	68	-6	27	29	2
7	HIIT	53	46	-7	17	16	-1
8	HIIT	50	50	0	19	17	-2
9	HIIT	48	46	-2	11	9	-2
11*	HIIT	45			25		
	Mean	54	52	-4	20	17	-1
	SD	10	9	3	6	17	2
3	CONT	68	28	-40	23	11	-12
4	CONT	48	43	-5	19	20	1
5	CONT	36	40	4	15	16	1
6	CONT	31	32	1	11	10	-1
10	CONT	51	61	10	34	32	-2
12*	CONT	76			36		
	Mean	52	41	-6	23	18	-3
	SD	18	13	20	10	9	5
	p			0.845			0.658

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; base: baseline; post: post –trial; diff: difference between baseline and post-trial
*No post intervention measurements for participants 11 or 12 as both dropped out.

There were no noticeable trends in the changes of the MSIS-29 psychological sub-scale scores in either training groups and there was no difference between the changes of the two groups (p=0.658). Participant 3 however, displayed large changes in both their physical and psychological impact scores; with a decrease of 40 in physical impact, and 12 in psychological impact. This was also the participant who had the largest decrease in their fatigue scores and a clinically significant improvement in their timed 25 foot walk test.

There was no trend in changes in anxiety scores observed in either training group and there was no difference between the changes in either group (p=0.683). This lack of trend and lack of difference was also observed when depression scores were examined (p=0.916) (Table 8-13). Participant 3, who reported the largest decreases in both their anxiety and depression scores, had abnormal scores at baseline and subsequently at post intervention was below the abnormal cut-off (<11 points) following the CONT intervention. This was also the participant who reported the large decrease in fatigue and MSIS-29 scores.

Table 8-13 Baseline, post-trial and difference between the measurements of the anxiety and depression sub-scales of the hospital and anxiety depression scale and the symbol digit modalities test for each participant

		Anxiety			Depression			SDMT		
Pt	Group	Base	Post	Base	Post	Diff	Diff	Base	Post	Diff
1	HIIT	7	9	2	4	4	0	57	59	2
2	HIIT	11	9	-2	8	11	3	33	39	6
7	HIIT	6	6	0	5	6	1	34	37	3
8	HIIT	8	4	-4	0	6	6	28	29	1
9	HIIT	3	1	-2	5	3	-2	43	48	5
11*	HIIT	12			10			48		
	Mean	8	6	-1	5	6	2	41	42	3
	SD	3	3	2	3	3	3	11	11	2
3	CONT	15	6	-9	11	5	-6	47	36	-11
4	CONT	7	6	-1	7	9	2	46	47	1
5	CONT	2	4	2	7	11	4	30	28	-2
6	CONT	6	1	-5	2	4	2	57	56	-1
10	CONT	3	5	2	5	7	2	15	25	10
12*	CONT	9			9			15		
	Mean	7	4	-2	7	7	1	35	38	-1
	SD	5	2	5	3	3	4	18	13	8
	p			0.683			0.916			0.284

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; base: baseline; SDMT: symbol digit modalities test; post: post –trial; diff: difference between baseline and post-trial
*No post intervention measurements for participants 11 or 12 as both dropped out.

In the HIIT group all participants increased their SDMT score post intervention (range 1 - 6) (Table 8-13) but only two people in the CONT group had increased scores (range -11 to 10). There was no difference between the changes in the two groups (p= 0.284). However, when participant 10 was removed from the analysis, the difference was significant (p=0.036) (result not in table). This may indicate that HIIT had a positive effect on mental processing speed and that CONT did not have an effect. However, previous research has reported that changes in the SDMT are only likely to be clinically significant if they are of 8 or more and convincing if 12 or more (Benedict et al., 2012). Therefore despite this increase in mental processing speed across the HIIT group it was unlikely to be clinically significant.

8.19.3 Physiological outcomes

There was no noticeable trend in the changes of resting levels of BDNF in the HIIT group, but there was a trend towards an increase in the CONT group as four participants increased their levels (range -2.69 - 14.08 ng/ml) (Table 8-14). There were however, no differences in the changes between the two training groups (p=0.761).

There were no noticeable trends in non-fasting triglyceride levels or total cholesterol in either the HIIT or the CONT group. There were also no differences in changes between the two training groups in either non-fasting triglyceride levels (p=0.754), or total cholesterol (p=0.745) (Table 8-15). Most participants however, already had healthy baseline measurements. One participant did display a large increase in their non-fasting triglyceride levels of an increase of 2.4 mmol/l but this participant also had a high baseline non-fasting triglyceride level over 3.0 mmol/l at baseline (Table 8-15).

Table 8-14 Baseline, post-trial and difference between the measurements of concentrations of brain derived neurotrophic factor for each participant

		BDNF concentration (ng/ml)		
Pt	Group	Base	Post	Diff
1	HIIT	19.6	44.11	24.51
2	HIIT	41.03	38.34	-2.69
7	HIIT	36.14	40.09	3.95
8	HIIT	34.81	22.55	-12.26
9	HIIT	44.91	46.24	1.33
11*	HIIT	29.68		
	Mean	34.36	38.27	2.97
	SD	8.93	9.33	13.52
3	CONT	50.18	53.45	3.27
4	CONT	31.74	45.82	14.08
5	CONT	37.99	47.97	9.98
6	CONT	36.12	37.00	0.88
10	CONT	33.33	30.64	-2.69
12*	CONT	40.83		
	Mean	38.37	42.98	5.10
	SD	6.64	9.09	6.82
	p			0.761

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; BDNF: brain derived neurotrophic factor; base: baseline; post: post – trial; diff: difference between baseline and post-trial.
*No post intervention measurements for participants 11 or 12 as both dropped out.

Table 8-15 Baseline, post-trial and difference between the measurements of concentrations of triglyceride, and total cholesterol for each participant

		Triglyceride			Total cholesterol		
Pt	Group	Base	Post	Diff	Base	Post	Diff
1	HIIT	0.9	1.3	0.5	5.1	6.0	0.9
2	HIIT	0.6	0.7	0.1	5.1	5.2	0.1
7	HIIT	2.3	2.1	-0.2	6.8	6.4	-0.4
8	HIIT	1.6	1.5	-0.1	4.5	4.8	0.2
9	HIIT	1.4	1.5	0.1	7.0	7.1	0.1
11*	HIIT	2.5			5.7		
	Mean	1.5	1.4	0.1	5.7	5.9	0.2
	SD	0.7	0.5	0.3	1.0	0.9	0.5
3	CONT	1.5	1.8	0.9	7.2	7.8	0.6
4	CONT	1.5	0.7	-0.8	4.7	4.5	-0.2
5	CONT	1.5	2.0	0.5	5.2	5.2	0.0
6	CONT	3.5	5.9	2.4	5.9	6.0	0.1
10	CONT	2.9	2.5	-0.4	5.9	6.7	0.8
12*	CONT	1.3			6.2		
	Mean	2.0	2.6	0.4	5.8	6.0	0.3
	SD	0.9	2.0	1.3	0.8	1.3	0.5
	p			0.754			0.745

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; SD: standard deviation; base: baseline; post: post –trial; diff: difference between baseline and post-trial; HDL: high density lipoprotein
*No post intervention measurements for participants 11 or 12 as both dropped out.
All measurements are in mmol/l.

There was no trend observed in the changes of HDL concentrations in either the HIIT or the CONT groups and there was no difference between the changes of the two training groups (p=0.383) (Table 8-16). These results indicate that neither HIIT nor CONT had an effect on HDL concentrations.

There was a trend towards an increase in non-HDL cholesterol levels in both the HIIT and the CONT groups as in both groups four out five participants displayed an increase. However, as with the other lipoprotein measurements, there was no difference between the changes of the two training groups (p=0.712) (Table 8-16).

Table 8-16 Baseline, post-trial and difference between the measurements of concentrations of high density lipoprotein and non-high density lipoprotein cholesterol for each participant

		HDL			Non-HDL cholesterol		
Pt	Group	Base	Post	Diff	Base	Post	Diff
1	HIIT	1.8	2.0	0.2	3.3	4.1	0.8
2	HIIT	1.9	1.6	-0.3	3.2	3.6	0.4
7	HIIT	1.3	1.2	-0.1	5.6	5.1	-0.5
8	HIIT	0.9	1.1	0.2	3.6	3.7	0.1
9	HIIT	1.6	1.5	-0.1	5.4	5.6	0.2
11*	HIIT	1.2			4.5		
	Mean	1.5	1.5	-0.05	4.2	4.4	0.2
	SD	0.4	0.3	0.2	1.2	0.9	0.5
3	CONT	0.9	0.8	0.1	6.2	7	0.8
4	CONT	1.6	1.7	0.1	3.1	2.8	-0.3
5	CONT	1.5	1.5	0.0	3.7	3.7	0.0
6	CONT	0.8	0.7	-0.1	5.1	5.3	0.2
10	CONT	1.1	1.1	0.0	4.8	5.7	0.9
12*	CONT	1.3			4.9		
	Mean	1.2	1.2	0.04	4.6	4.9	0.3
	SD	0.3	0.4	0.1	1.2	1.7	0.5
	p			0.373			0.712

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; SD: standard deviation; base: baseline; post: post –trial; diff: difference between baseline and post-trial; HDL: high density lipoprotein
*No post intervention measurements for participants 11 or 12 as both dropped out.
All measurements are in mmol/l.

There was no noticeable trend in changes in resting lactate concentrations of either the HIIT or the CONT groups and no difference between the changes of either training group (p=0.465) (Table 8-17). Similarly, there was no trend in changes in peak lactate in either the HIIT or the CONT groups and there was no difference between the changes of the training groups (p=0.309) (Table 8-17). However, the number of participants who reached a peak lactate greater than 8.0 mmol/l, indicating maximal exertion (Midgley et al., 2007, Thompson et al., 2000), rose from two (pre-intervention) to three (post-intervention) in the CONT group and three to four in the HIIT group. This may indicate that 8 weeks of

aerobic training, regardless of whether it is HIIT or CONT can increase the likelihood of reaching maximal exertion during testing.

Table 8-17 Baseline, post-trial and difference between the measurements of concentrations of resting and peak lactate for each participant

		Resting lactate			Peak lactate		
Pt	Group	Base	Post	Diff	Base	Post	Diff
1	HIIT	0.6	0.8	0.2	6.2	6.3	0.1
2	HIIT	0.8	1.7	0.9	4.6	9.8	5.2
7	HIIT	5.4	1.2	-4.2	11.6	9.5	-2.1
8	HIIT	1.0	2.2	1.2	15.5	13.4	-2.1
9	HIIT	1.5	2.2	0.7	12.4	11.0	-1.4
11*	HIIT	1.7			4.4		
	Mean	1.8	1.6	-0.2	9.1	10.0	0.8
	SD	1.8	0.6	2.2	4.7	2.6	3.0
3	CONT	5.6	1.1	-4.5	7.8	9.0	1.2
4	CONT	4.5	6.9	2.4	18.5	12.4	-6.1
5	CONT	4.8	2.4	-2.4	6.0	3.4	-2.6
6	CONT	2.1	1.3	-0.8	8.1	9.3	1.2
10	CONT	2.5	3.1	0.6	4.3	3.9	-0.4
12*	CONT	2.1			3.8		
	Mean	3.6	3.0	-0.9	8.1	7.6	-1.6
	SD	1.6	2.4	2.7	5.4	3.9	3.5
	p			0.465			0.309

Abbreviations: pt: participant number; HIIT: high intensity interval training; CONT: continuous moderate intensity training; SD: standard deviation base: baseline; post: post –trial; diff: difference between baseline and post-trial
*No post intervention measurements for participants 11 or 12 as both dropped out.

8.20 Effect sizes of significant results

There were only two instances of statistically significant differences in changes between the two groups. These were in HRMax (p=0.013) (Table 8-18) and in SDMT scores when participant 10 was removed as an outlier (p=0.036) (Table 8-19). There were no other statistically significant differences in changes

between the two groups both when participant 10 was included and excluded (Table 8-18, Table 8-19).

After the intervention, the HIIT group increased their HRMax by a mean of 16 bpm (SD 3), with a large effect size (Cohen's *d*=1.67) and the CONT group decreased their HRMax by 3 bpm (SD10) with a weak effect size (Cohen's *d*=-0.13). This indicates that HIIT had a beneficial effect on the group's HRMax while there was no difference in the CONT group.

After the intervention the HIIT group increased their SDMT score by a mean 3 points (SD 2), with a moderate effect size (Cohen's *d*= 0.67), while the CONT group worsened their score by a mean of -1 point (SD 8) with a weak effect size (Cohen's *d*= -0.09). These changes were however, small and below the threshold of a likely clinically significant change of 8 or more (Benedict et al., 2012).

Table 8-18 Baseline, post intervention and difference from baseline measurements of cardiovascular risk factors and physiological outcomes for both training groups

	HIIT			CONT				
	Pre	Post	Diff	Pre	Post	Diff	*p* (n=10)	*p* (n=9)
Resting HR (bpm)	69 (8)	66 (5)	-2 (9)	80 (10)	74 (9)	-5 (10)	0.605	0.67
Systolic (mm/Hg)	126 (11)	143 (9)	18 (15)	127 (9)	129 (17)	3 (8)	0.089	0.135
Diastolic (mm/Hg)	78 (11)	82 (15)	4 (7)	77 (6)	77 (9)	2 (7)	0.649	0.914
Resting Lactate (mmol/l)	1.83 (1.80)	1.62 (0.62)	-0.24 (2.24)	3.60 (1.55)	2.96 (2.35)	-0.94 (2.66)	0.465	0.462
HRMax (bpm)	132 (11)	147 (12)	16 (3)	150 (28)	153 (36)	-3 (10)	0.013*	0.001*
Peak lactate (mmol/l)	9.1 (4.7)	10.0 (2.6)	0.8 (3.0)	8.1 (5.4)	7.6 (3.9)	-1.6 (3.5)	0.309	0.309
TG (mmol/l)	1.5 (0.7)	1.4 (0.5)	0.1 (0.3)	2.0 (0.9)	2.6 (2.0)	0.4 (1.3)	0.754	0.327
Chol (mmol/l)	5.7 (1.0)	5.9 (0.9)	0.2 (0.5)	5.8 (0.8)	6.0 (1.3)	0.3 (0.5)	0.745	0.899
HDL (mmol/l)	1.5 (0.4)	1.5 (0.3)	-0.05 (0.2)	1.2 (0.3)	1.2 (0.4)	0.04 (0.1)	0.373	0.383
Non-HDL chol (mmol/l)	4.2 (1.2)	4.4 (0.9)	0.2 (0.5)	4.6 (1.2)	4.9 (1.7)	0.3 (0.5)	0.712	0.939
BDNF (ng/ml)	34.36 (8.93)	38.27 (9.33)	2.97 (13.52)	38.37 (6.64)	42.98 (9.09)	5.1 (6.82)	0.761	0.596

Abbreviations: HR: heart rate; HRMax: maximal heart rate; TG: triglyceride; chol: cholesterol; HDL: high density lipoprotein; BDNF: brain derived neurotrophic factor; HIIT: high intensity interval training; CONT: continuous moderate intensity training; base: baseline; post: post –trial; diff: difference between baseline and post-trial

All figures are mean (standard deviation). All difference values are post-intervention value minus pre-intervention value. All tests were independent t tests between the means of the difference between pre and post intervention apart from the testing of resting lactate and TG which were Mann-Whitney tests due to non-normal distribution.

* Statistically significant <0.05

Table 8-19 Baseline, post intervention and difference from baseline measurements of multiple sclerosis clinical outcome measures for both training groups

	HIIT			CONT				
	Pre	Post	Diff	Pre	Post	Diff	*p* (n=10)	*p* (n=9)
T25FW	9.5 (6.6)	8.4 (3.4)	-1.7 (3.9)	12.4 (7.2)	11.5 (8.0)	-1.0 (1.6)	1.000	0.712
MSIS-29 Phys	54 (10)	52 (9)	-4 (3)	52 (18)	41 (13)	-6 (20)	0.845	0.61
MSIS-29 Psych	20 (6)	17 (17)	-1 (2)	23 (10)	18 (9)	-3 (5)	0.658	0.662
HADS Anxiety	8 (3)	6 (3)	-1 (2)	7 (5)	4 (2)	-2 (5)	0.683	0.421
HADS Depress	5 (3)	6 (3)	2 (3)	7 (3)	7 (3)	1 (4)	0.916	1.000
FSMC Total	74 (15)	72 (23)	-3 (9)	73 (29)	61 (23)	-7 (13)	0.621	0.513
FSMC Motor	38 (7)	36 (10)	-2 (3)	39 (12)	33 (10)	-4 (7)	0.695	0.591
FSMC Cog	36 (8)	37 (14)	0 (5)	34 (17)	28 (13)	-3 (6)	0.474	0.412
SDMT	41 (11)	42 (11)	3 (2)	35 (18)	38 (13)	-1 (8)	0.284	0.036*

Abbreviations: T25FW: timed 25 foot walk test; MSIS-29: multiple sclerosis impact scale; n: number; Phys: physical sub-scale; Psych: psychological sub-scale; HADS: hospital anxiety and depression scale; FSMC: fatigue scale for motor and cognitive function; Cog: cognitive; SDMT: symbol digit modalities test; HIIT: high intensity interval training; CONT: continuous moderate intensity training; base: baseline; post: post –trial; diff: difference between baseline and post-trial
All values are mean (standard deviation). All testing was independent t tests of differences in baseline and post intervention values apart from timed 25 foot walk test and the HADS depression sub-scale which were Mann-Whitney due to non-normal distribution.
* Statistically significant at $p<0.05$

8.21 Summary of results

In summary, these results demonstrate that HIIT was well tolerated in people with progressive MS and is a feasible intervention to use in the rehabilitation of this patient group. Adherence to, and compliance with, the protocol was high, and participants in the HIIT group experienced no adverse events while there were three adverse events in the CONT group. In addition both HIIT and CONT were well tolerated as there was no adverse impact on the participants' MS symptoms.

The small sample of completing participants (n=10) and large standard deviations in the outcomes meant although there were some trends in the results, with two exceptions, there were no statistically significant differences between the changes of the two groups pre and post intervention.

The participants who received the HIIT intervention demonstrated a significant improvement in their HRMax compared to the CONT group. In both groups there was a higher number of participants reaching maximal exertion, as measured by peak lactate. This may indicate a learning effect because prior to the intervention just one participant had experience in maximal exertion tests.

A statistically significant difference was also found between the HIIT and CONT groups in mental processing speed (SDMT). However, this difference is likely due to an outlier who had poorer scores after the intervention in the CONT group and differences were not clinically significant.

8.22 Discussion

Overall this study showed that the implementation of HIIT is feasible in people moderately affected by progressive MS as adherence was high at 98.8%, overall compliance with the protocol was high at 89.6% and was 100% with the HIIT protocol, there were only two participants who dropped out, and there were only three adverse events which were all in the CONT group. Furthermore when compared to CONT, participants who received HIIT, increased their HRMax and their mental processing speed. The high rate of adherence and compliance add

to the case of HIIT being an appropriate modality for training people with MS. It has previously been stated that HIIT may be an appropriate modality because of the high energy expenditure in a short period of time and that the rest periods decrease the chance of thermosensitive symptoms in people with MS (Dalgas et al., 2008).

This HIIT study was only the second to solely include people with progressive MS, and the first to use cycle ergometry in a sample only with progressive forms of the disease. Similar to previous studies in this area the control group was a form of continuous moderate intensity exercise (Collett et al., 2011, Collett et al., 2017, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zimmer et al., 2017). The HIIT protocol of 6 x 90 seconds at 80-95% HRMax produced a total time of 144 minutes spent at a high intensity workload over the whole intervention. This is higher than three of the previous HIIT studies (Collett et al., 2011, Feltham et al., 2013, Zaenker et al., 2016, Skjerbæk et al., 2014), one of which found an improvement in VO_2peak (median 8.05 - 9.2ml/kg, p=0.05) (Collett et al., 2011, Feltham et al., 2013) and one in VO_2peak (+13.5%, p<0.0001) and HRMax (+3.73%, p=0.0120) (Zaenker et al., 2016).

It is interesting that the only other study to investigate HIIT in people with progressive MS did not find improvements (Skjerbæk et al., 2014). However, Skjerbæk et al. (2014), used arm ergometry, had a lower total high intensity worktime of 60 minutes, and included participants with a higher level of disability (EDSS 6.0-8.0). It is unclear whether any of these three differences of using arm ergometry, higher disability level and lower total worktime are the reason that improvements were not found in the sample of Skjerbæk et al. (2014). However, it should be noted that both this present study and the study by Skjerbæk et al. (2014) were not sufficiently powered meaning that any lack of result should be treated with caution.

8.22.1 The effect of high intensity interval training on maximal heart rate

An increase in HRMax was observed in the HIIT group and not in the CONT group. Five out of the six previous studies which investigated the effects of HIIT on

fitness, in people with MS, reported increases in a related outcome (Collett et al., 2011, Farup et al., 2016, Feltham et al., 2013, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016, Zimmer et al., 2017, Bansi et al., 2017, Keytsman et al., 2017). Two of these were in HRMax (Farup et al., 2016, Wens et al., 2015, Wens et al., 2017, Zaenker et al., 2016) and two were VO_2max (Collett et al., 2011, Feltham et al., 2013, Zimmer et al., 2017, Bansi et al., 2017). The only other study to investigate HIIT just in people with progressive MS did not find an increase in either HRMax or VO_2max (Skjerbæk et al., 2014). The differences in methodology between this present study and the study by Skjerbæk et al. (2014) have already been discussed above.

It was interesting that the CONT group did not show any improvement in their HRMax as a recent meta-analysis found that exercise had a moderate effect on fitness related outcomes in people with MS (Platta et al., 2016). The authors did note however, that intensities in the 20 studies included varied greatly or were poorly described. The lack of improvements in this study by the CONT group may have been due to the general deconditioning in the group which meant that two participant's resting HR was in their 60-70% HRMax training zone and one participant had a resting HR within 8 bpm of their training zone. Indeed, higher intensity training is linked to greater improvements in fitness in healthy individuals (Fleg, 2016).

Improvements in HRMax of HIIT group could have been generated by the higher level of energy expended due to Excess Post-exercise Oxygen Consumption (Tremblay et al., 1994, Gaesser and Brooks, 1984). This latter theory is strengthened by the study by Zimmer et al. (2017) and Bansi et al. (2017), who compared HIIT to CONT of an equal energy output and found that both groups increased their fitness when measured by VO_2max.

8.22.2 The effect of high intensity interval training on mental processing speed

When the outlier participant 10, was removed, there was a difference between the changes of HIIT and CONT groups in mental processing speed as measured by

the SDMT. The improvements noted were however, overall quite small (mean +3 points SD 2) and unlikely to be clinically significant as the Brief International Cognitive Assessment for MS committee stated that an increase of 8 points or more was likely to be clinically significant (Benedict et al., 2012). The only other study investigating the effect of HIIT on mental processing speed found that there was a time effect on SDMT scores but no time x group effects (Zimmer et al., 2017, Bansi et al., 2017). A systematic review examining the effect of exercise on cognition in people with MS found the evidence to be inconclusive (Sandroff et al., 2016). The authors reported that just one of the studies reviewed showed improvements in mental processing speed after 8 weeks of thrice weekly, 60 minute sessions of aerobic, balance and flexibility exercises (Sangelaji et al., 2015). Indeed an RCT by Coote et al. (2017), compared group exercise and education to group exercise and social cognitive therapy, and found increases in mental processing speed only in the social cognitive therapy group indicating that the effect was not from the exercise component. The fact that the present trial and previous HIIT research (Bansi et al., 2017, Zimmer et al., 2017) found positive effects on mental processing may indicate that beneficial effects can be produced using exercise of a higher intensity. Furthermore it may indicate that benefits can be elicited as good as or more than CONT. Further investigation by fully powered RCTs is warranted to confirm or deny this.

8.22.3 The effect of high intensity interval training on resting heart rate and blood pressure

This was only the second HIIT study to use resting HR an outcome measure, but found no effect from either HIIT or CONT. The cohort trial by Keytsman et al. (2017) found a decrease in resting HR after 12 weeks of combined HIIT, CONT and resistance training. Differences in results may have been due to the trial by Keytsman et al. (2017) having a longer intervention and also incorporating a resistance training element. Furthermore all participants in the present study had progressive MS and were moderately affected by their MS, while Keytsman et al. (2017) included participants who were mildly affected (EDSS<3.0) and did not report on MS type. Further investigation is warranted with a powered sample

size to establish if these variables are factors in the lack of effect found in this present study.

Two previous studies investigated the effects of HIIT on blood pressure in people with MS (Collett et al., 2011, Feltham et al., 2013, Keytsman et al., 2017). Like this present study no effect was observed. This lack of effect may have been because all three samples had blood pressures within a healthy range (Collett et al., 2011, Feltham et al., 2013, Keytsman et al., 2017). Uncontrolled high blood pressure was an exclusion criterion from taking part in this study, and while it was not in the other two previous studies. This may indicate that neither HIIT nor CONT have an effect on blood pressure, in people with MS, when it is in a healthy range. Further research should however investigate the effect of HIIT on blood pressure when it is in an unhealthy range.

8.22.4 The effect of high intensity interval training on brain derived neurotrophic factor

This study found that there was no effect of training on resting serum BDNF levels in either the HIIT or the CONT group. As was discussed in section 7.3.2 the evidence for using aerobic training to increase resting BDNF levels, in people with MS, is inconclusive. Of note all studies that included people with progressive MS, including the current study, did not report an increase in resting BDNF levels after receiving a training intervention. Also, this cohort's baseline concentration of BDNF was higher than the baseline concentrations reported in the previous studies investigating the effects of exercise on BDNF levels in people with MS as the highest concentration reported was 24.70 ng/ml SD 13 (Zimmer et al., 2017). There are however, a number of factors that could have affected this, including influences from disease and lifestyle (Bus et al., 2011) and also the ELISA kit used to measure the concentration (Polacchini et al., 2015). While the effect of training on BDNF levels is well established in healthy individuals (Dinoff et al., 2016), the evidence for the effect of exercise training on resting levels of BDNF remains inconclusive in people with MS but there is an indication that it may not have an effect on people with progressive MS. However, no studies to date have included a power calculation specifically for

BDNF. Further investigation should be carried out with suitably powered samples to establish if aerobic training does or does not have an effect on resting BDNF levels in people with progressive MS.

8.22.5 The effect of high intensity interval training on lipids

This was the first RCT, and second interventional study, to examine the effect of aerobic exercise on lipid profiles in people with MS and no effect was observed on levels of non-fasting triglyceride, HDL, total cholesterol and non-HDL cholesterol. The results of this trial were similar to that of Keytsman et al. (2017) who, after 12 weeks of HIIT and resistance training, also did not observe any changes in the lipid profiles of their participants. A review by Wens et al. (2013) concluded that it was unclear whether people with MS were at risk of developing cardiovascular disease from dyslipidemia because evidence was conflicting. A study by White et al. (2006) found that eight weeks of progressive resistance training, in moderately disabled people with MS, had no effect on triglyceride, HDL or total cholesterol. A cohort study investigating the links between physical activity and cholesterol and triglyceride levels found that triglyceride levels were lower in people that exercised but there was no association with cholesterol levels (Slawta et al., 2002). However, similar to the sample included by Keytsman et al. (2017), most of the participants in this present sample were not in dyslipidemia at baseline. Similar to the effects of blood pressure and resting heart rate, further investigation is warranted in people with MS, who are in dyslipidemia, to establish if HIIT has a beneficial effect.

8.22.6 The effect of high intensity interval training on gait speed

There were no changes in walking speed in either the HIIT or the CONT groups, although there were some clinically significant changes at individual levels. Only one previous HIIT study examined walking in the form of the 2 min walk test (Collett et al., 2011, Feltham et al., 2013). The results of this test, which

technically examines sub-maximal endurance, found an increase in both the HIIT and CONT groups. These improvements were also maintained at the 12 week follow up period after the intervention had finished. This may indicate that an exercise programme, regardless of it is CONT or HIIT could have a beneficial effect on walking endurance, but not gait speed.

A recent meta-analysis of studies which examined the effect of exercise on walking in all people with MS found an overall positive effect (Pearson et al., 2015). Analysis by the authors found that although there was a positive response to walking speed from aerobic, resistance training and yoga when delivered individually, but the greatest benefits were found in interventions which combined both aerobic and resistance training (Pearson et al., 2015). This may explain the lack of results in this study as only one type of training was employed.

8.22.7 The effect of high intensity interval training on fatigue

This study found no impact from either training protocol on the fatigue of participants. This is in line with two previous HIIT studies which measured fatigue that similarly found no differences between their intervention and control groups (Collett et al., 2011, Feltham et al., 2013, Skjerbæk et al., 2014). As was stated in the systematic review (section 7.13) one study used the Fatigue Severity Scale (Collett et al., 2011, Feltham et al., 2013) which has limitations in people with MS and one study used a sample that was not severely fatigued (Skjerbæk et al., 2014). In general the evidence for using exercise to improve fatigue in people with MS is positive, but weak (Heine et al., 2015). This 2015 Cochrane review called for more exercise studies involving participants who were severely fatigued. As measured by the FSMC, the participants in the present study were severely fatigued, and while improvements were noted in some individuals, there was not a change across the training groups. Further research on the effects of HIIT on fatigue in people with MS is needed.

8.22.8 The effect of high intensity interval training on impact of disease

The present study found no improvement in disease impact measures. The two previous studies that have examined the effect of HIIT on quality of life in people with MS found conflicting results. One measured an improvement (Zaenker et al., 2016) and one measured a deterioration (Collett et al., 2011, Feltham et al., 2013). The study which reported an improvement also had a resistance and CONT element in their protocol making it difficult to attribute any changes to the HIIT element. Other research examining the effect of exercise on quality of life in people with progressive MS, found that a 12 week training protocol of aerobic training three times a week, of either body weight supported treadmill training or recumbent stepping produced improvements when measured by the Multiple Sclerosis Quality of Life – 54 questionnaire (Pilutti et al., 2016). Furthermore, two RCTs investigating resistance training in people with MS both found improvements in quality of life (Dalgas et al., 2010, Dodd et al., 2011). However, only one of these studies found that their improvements were maintained at a three month follow up period (Dalgas et al., 2010). These, conflicting results in the literature and the results from the current study highlight that further research is needed. The study by Pilutti et al. (2016) involved people with progressive MS with severe disability, while Dalgas et al. (2010) and Dodd et al. (2011) involved people with RRMS and moderate disability. Similarly the studies by Zaenker et al. (2016), Collett et al. (2011) and Feltham et al. (2013) included moderately disabled patients who did not have progressive forms of the disease. The limited evidence to date would indicate that neither disability nor type of MS is a factor affecting the effect of exercise on quality of life in people with MS.

8.22.9 The effect of high intensity interval training on anxiety and depression

There was no effect on anxiety or depression in either training group. To date there has been only one other HIIT study in MS that measured depression as an outcome measure (Skjerbæk et al., 2014) and none that measured anxiety. Skjerbæk et al. (2014) also found that there was no effect of HIIT on depression

when measured using the Major Depression Inventory. This may indicate that the use of HIIT may not be effective in reducing anxiety or depression in people with progressive MS. However, neither the study by Skjerbæk et al. (2014) nor the present study, were sufficiently powered.

In the general population exercise has been shown to have a positive effect on both depression and anxiety but the effect size was higher in depression (Wegner et al., 2014). However, previous research investigating the effect of exercise on anxiety and depression in people with MS is conflicting. The study by Coote et al. (2017) which compared the effects of 10 weeks of group exercise combined with education relating to physical activity and group exercise combined with social cognitive theory, in people with MS, only found improvements in depression in the social cognitive theory group. While Aydin et al. (2014) reported that a 12 week programme of hospital based calisthenics, five times a week, improved anxiety but not depression. Conversely the RCT by Dalgas et al. (2010) found improvements in depression scores following a 12 week resistance training programme. However, all three of these studies used moderately disabled people with RRMS. The lack of significant results from this study and conflicting results from previous studies, create the need for further investigation especially in people with progressive MS.

8.22.10 The effect of high intensity interval training on lactate levels

There were no differences in changes in resting or peak lactate concentrations after the intervention. This was an unexpected result as overall HRMax rose in the HIIT group indicating an increase in fitness and work rate during the maximal exertion test. However, even though there was no difference at a group level, the number of participants with results above the 8.0 mmol/l threshold, indicating maximal exertion, increased from two to three in the CONT group and three to four in the HIIT group. The two participants with the highest peak lactate at baseline also had the lowest EDSS scores of 4.0 and 4.5. This was expected, as previous research has shown that as EDSS scores rise, the likelihood of reaching maximal aerobic capacity decreases, and patients are more likely to

stop due to symptomatic reasons such as muscle fatigue in affected limbs (Romberg et al., 2004). However, the measurement of exertion by lactate in people with MS has been criticised, as people with MS have higher concentrations of resting lactate and this is particularly more prevalent in people with progressive forms of the disease (Amorini et al., 2014). Indeed the resting lactate level of this sample was 2.7 (SD 1.8) mmol/l at baseline which puts the resting concentrations above that of normal reported levels in untrained healthy individuals of 0.8-1.5 mmol/l (McArdle et al., 2006). This higher resting lactate may provide false positives for reaching maximal aerobic capacity as the work rate to reach 8.0 mmol/l could be less than if a participant had a lower resting lactate level.

8.22.11 Participant 10

In addition to receiving higher intensity than the protocol stated, participant 10 did not respond as expected during the post intervention measurements of her HRMax. This participant was very deconditioned at baseline, only being able to cycle for less than 5 minutes. Her HRMax at baseline was 124 bpm and over the 8 weeks she improved her endurance and was able to cycle for the full 30 minutes. During this time her average working HR dropped from 88% to 78% of HRMax. Post intervention she cycled for longer than baseline, reached a higher resistance, but had a lower HRMax (124 to 105 bpm), lower peak lactate (4.3 to 3.9 mmol/l) and lower difference in lactate (1.8 to 0.8 mmol/l). There are a number of possible reasons for this spurious result. Firstly, that her heart, for some reason, did not respond to the increased workload and oxygen demands placed on it. Secondly there was a malfunction with the HR monitor, which had happened occasionally during the intervention. Thirdly, there was human error in the delivery of the test. However, as both physiological measures of the HRMax and lactate response indicate that this participant did not work as hard during her post intervention maximal test, this would indicate human error.

8.22.12 Limitations

Originally, it had been planned to use a repeated two way measure analysis of variance to explore differences between the two training groups. However, due to recruitment issues, the total completed sample of just five participants in each group meant that this form of analysis was not appropriate. Furthermore while a matched pair randomisation design controlling for fatigue, gender, age, EDSS level and baseline fitness was highly desirable, this was not appropriate with the small sample obtained. The small sample size and lack of power may be why some of the outcome measures utilised did not reach statistical significance despite an indication of a trend of change. Lastly there was no blinding of the assessor, which could have potentially led to bias of results.

8.22.13 Recommendations for future research

Recommendations for research have already been identified. A fully powered RCT in a similar sample of people with progressive MS is warranted to strengthen the results found in this study. Furthermore, future research should also investigate if it is feasible to use arm ergometry to improve fitness in people with MS. As this study and all others before which used a progressive sample, did not find a positive result, a comparison of the effects of exercise on BDNF, resting heart rate, blood pressure, blood lipids, fatigue, anxiety and depression levels, by MS type should be carried out to explore the potential effect of this variable.

8.22.14 Relevance for clinicians and people with Multiple Sclerosis

Due to small numbers recruited, the generalisability of the results from this study remain limited. However, when the results of this trial are combined with the rest of the literature, presented in sections 7.13-7.14, this trial adds to this body of evidence, reaffirming the positive results found that HIIT is both a safe and feasible intervention that can be used for aerobic training in people with MS

who are mildly, moderately or severely disabled. Clinicians should consider the use of HIIT in their management of their patients, and people with MS should approach HIIT with confidence that it is safe and a more efficient training method than traditional continuous aerobic training.

8.22.15 Conclusions

Overall, this study indicates that HIIT is a feasible intervention to use in people with progressive MS and an EDSS range of 4.0-6.0. Furthermore, improvements were observed in the HIIT group in HRMax and mental processing speed indicating that HIIT may be a more appropriate intervention to elicit improvements in these areas. Further investigation through a fully powered RCT is warranted in this patient group.

Chapter 9 Final conclusions and recommendations

The overall aim of this research was to investigate the use of physiotherapy for people with progressive MS by evaluating the current literature, surveying the patient population in regard to their use of services, and assess the feasibility of High Intensity Exercise Training (HIIT) which was not previously investigated in moderately disabled people with progressive MS. This aim was formulated to address gaps in the literature and was driven by calls for investigation and further research into the benefits of physiotherapy in people with progressive MS (Fox et al., 2012, MS Society, 2014).

9.1 Original contribution of studies

All three studies make an original contribution to knowledge in the field of rehabilitation of people with progressive MS. The systematic review reported in Chapter 3 was the first to assess the available literature for the efficacy of using physiotherapy in the rehabilitation of people with progressive MS. The online survey conducted included the largest sample only of people with progressive MS, and was the first to assess the level of access and use of clinical services at a national level in the United Kingdom. The feasibility study was the first to explore the use of HIIT in people moderately affected by progressive MS. It was also the first to explore the use of cycle ergometry as the mode for delivering HIIT in a sample solely of people with progressive MS.

9.2 Overall conclusions and recommendations

The aim of the systematic review was to assess the efficacy of using physiotherapy in the rehabilitation of people with progressive MS. The outcome of the review demonstrated positive, but weak, evidence for the use of physiotherapy in the rehabilitation of people with progressive MS. It highlighted that, to improve the evidence base, studies with more robust methodologies

were required in this area, specifically fully powered randomised controlled trials.

The aim of the online survey was to investigate the level of access to, delivery of, barriers to access, and opinion of physiotherapy services by people with progressive MS in the UK, along with the level of access to MS Specialists, a regular review, use of clinical services and the use of complementary and alternative therapies. The results of the survey revealed a high rate of access to MS Specialists across the United Kingdom, but almost a quarter were not receiving a regular review. It is recommended that service providers should aim to address this gap. Access to physiotherapy was also high and as a discipline, was well perceived among respondents with 70% reporting it had a positive effect on their MS. The most commonly prescribed interventions were supervised and unsupervised exercise. Delivery of physiotherapy closely matched desired delivery however there was a desire for more home-based care. Although it is recognised that home based care is more expensive than out-patient care it is recommended that service providers should investigate the feasibility of providing home-based care for those in need. This was also a recommendation of the UK MS Society (MS Society, 2016b).

The aim of the intervention study was to explore the feasibility of using HIIT in moderately disabled people with progressive MS. Furthermore this study also explored the effects of HIIT, compared to continuous moderate intensity training, on physiological and MS clinical outcomes in people with progressive MS. High Intensity Interval Training was found to be a feasible modality of aerobic training for people with progressive MS. As an intervention, HIIT was found to be very well tolerated and acceptable with a high adherence and compliance rate and no adverse in the HIIT group. Furthermore, participants receiving HIIT improved their maximal heart rate and mental processing speed while no significant improvements were found in the group receiving continuous training. As HIIT takes less time than continuous training and allows for working at high intensities while avoiding thermosensitive reactions, this suggests that HIIT may be a practical and effective intervention in eliciting health benefits in people with progressive MS. However, a fully powered trial is required to confirm or deny this result.

In conclusion while each of the three studies produced positive results, overall further research is required to strengthen or confirm the findings. As such, the work contained within this thesis should be viewed as the groundwork to be built upon for further research or service improvement. As was stated in Chapter 1, the three studies in this thesis may be of interest to different audiences and therefore the recommendations for further research or service implementation from each study (sections 3.5.2, 6.9 and 8.22.13) may be more applicable for these specific audiences. However, despite the need for further work this body of research has shown that physiotherapy has the potential to be beneficial for people with progressive MS, that people with progressive MS in the UK are engaging with physiotherapy as a discipline, and that new interventions such as HIIT hold promising results for improving health of this patient group.

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Appendices

Appendix 1 – Physiotherapy rehabilitation for people with progressive Multiple Sclerosis: a systematic review

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Archives of Physical Medicine and Rehabilitation 2016;97:141-51

REVIEW ARTICLE

Physiotherapy Rehabilitation for People With Progressive Multiple Sclerosis: A Systematic Review

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Abstract

Objective: To assess the efficacy of physiotherapy interventions, including exercise therapy, for the rehabilitation of people with progressive multiple sclerosis.

Data Sources: Five databases (Cochrane Library, Physiotherapy Evidence Database [PEDro], Web of Science Core Collections, MEDLINE, Embase) and reference lists of relevant articles were searched.

Study Selection: Randomized experimental trials, including participants with progressive multiple sclerosis and investigating a physiotherapy intervention or an intervention containing a physiotherapy element, were included.

Data Extraction: Data were independently extracted using a standardized form, and methodologic quality was assessed using the PEDro scale.

Data Synthesis: Thirteen studies (described by 15 articles) were identified and scored between 5 and 9 out of 10 on the PEDro scale. Eight interventions were assessed: exercise therapy, multidisciplinary rehabilitation, functional electrical stimulation, botulinum toxin type A injections and manual stretches, inspiratory muscle training, therapeutic standing, acupuncture, and body weight–supported treadmill training. All studies, apart from 1, produced positive results in at least 1 outcome measure; however, only 1 article used a power calculation to determine the sample size and because of dropouts the results were subsequently underpowered.

Conclusions: This review suggests that physiotherapy may be effective for the rehabilitation of people with progressive multiple sclerosis. However, further appropriately powered studies are required.

Archives of Physical Medicine and Rehabilitation 2016;97:141-51

Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease of the central nervous system resulting in gray matter and axonal loss.[1,2] Currently, there are an estimated 130,000 cases of MS in the United Kingdom, with an incidence of 11.52 per 100,000 women and 4.84 per 100,000 men.[3] Approximately 15% of all individuals with MS are diagnosed with primary progressive multiple sclerosis (PPMS), and 80% of those diagnosed with relapsing-remitting multiple sclerosis (RRMS) go on to develop secondary progressing multiple sclerosis (SPMS).[4] There is a strong evidence base for interventions for the treatment of people with RRMS; however, although studies are currently ongoing, there are limited effective treatments for people with progressive MS.[5] The International Progressive MS Alliance have highlighted this area as a priority, especially for those with a higher level of disability.[5]

There is a growing body of literature investigating the benefits of physiotherapy (a physical intervention that may be used by a physiotherapist, including physical activity and exercise interventions) in the rehabilitation of people with MS. In a series of review articles, exercise therapy and physical activity have been shown to be generally beneficial to those with MS who are not suffering a relapse[6-8] and to have positive effects on fatigue,[9,10] health-related quality of life,[11] and muscle strength[12] in those with a mild to moderate disability. Physiotherapy has also been shown to have a positive effect on balance and mobility.[13-15] However, when the level of disability increases, the efficacy of physiotherapy is less compelling.[13,15] Although some studies have considered their results in terms of disability levels, none have made a distinction between RRMS and progressive MS. To date, there has not been a published review examining the evidence for

Supported by the Bevan Studentship, NHS Ayrshire and Arran.
Disclosures: none.

0003-9993/15/$36 - see front matter © 2016 by the American Congress of Rehabilitation Medicine
http://dx.doi.org/10.1016/j.apmr.2015.07.022

physiotherapy for the rehabilitation of people with progressive MS. Consequently, the aim of this systematic review is to assess the efficacy of physiotherapy rehabilitation for people with progressive MS.

Methods

In December 2014 a search was conducted of the following electronic databases: the Cochrane Library, Physiotherapy Evidence Database (PEDro), Web of Science Core Collections, MEDLINE, and Embase. No restrictions were placed on publication date, and studies were limited to English language only. Individual search strategies were made up of keywords and Medical Subject Headings (table 1). Reference lists of relevant articles were also searched.

To be included in the review, articles had to be published in English, include solely participants with progressive forms of MS or where there was a combination of types of MS distinct results for the different types of MS are presented, evaluate a physiotherapy intervention(s) or an intervention containing a physiotherapy element, have randomized participants, have a comparison group, and use at least 1 objective outcome measure. Articles were excluded if they were nonhuman studies, conference abstracts, or posters. Articles were initially screened by title and abstract. Full articles were then read. When there was ambiguity in meeting the inclusion criteria, the authors were contacted for clarification.

Quality assessment (external validity, internal validity, reporting of statistics) was assessed using the PEDro scale, which has been shown to be reliable and valid in rating methodologic quality of studies.[16,17] The 11-point scale was given a score out of 10 (no point was awarded for the initial item of stating inclusion and exclusion criteria) as per the guidelines. Scoring was carried out by 3 reviewers (E.C., L.P., E.H.C.). A pilot quality assessment was conducted to ensure consistency, where all 3 reviewers read and independently scored 1 article; after this, scoring was discussed and agreed. Each article was then scored independently by 2 reviewers, and the scores were compared. When there was a discrepancy in the score, differences were agreed via discussion, which included the third reviewer. Quality assessment was entirely based on the content of the study in the published article. When 2 articles were from the same study but reported different outcome measures they were combined and considered as a single study. Data extraction was done independently using a standardized form into evidence tables. The following data were extracted: study design, sample size, dropout rate, type of MS of participants, Expanded Disability Status Scale (EDSS) range,[18] intervention type, length, frequency, setting, time points of measurement, control intervention, outcome measures, baseline measurements, and main findings.

List of abbreviations:

BTX-A	botulinum toxin type A
BWSTT	body weight–supported treadmill training
EDSS	Expanded Disability Status Scale
FES	functional electrical stimulation
MCID	minimum clinically important difference
MS	multiple sclerosis
PEDro	Physiotherapy Evidence Database
PPMS	primary progressive multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary progressing multiple sclerosis

Results

Outcome of search

From the electronic search 1027 articles were identified, and 4 articles were identified from relevant article's reference lists (fig 1). Of these, 197 were duplicates, leaving 834 unique publications for screening by title and abstract. After screening, 783 articles were excluded. Full texts of 51 articles were read, and 36 were excluded. From the remaining 15 articles, there were 2 instances of 2 articles that were from the same study but had used different outcome measures; they were therefore combined.[19-22] Therefore, 13 studies (published within 15 articles) were included within this review (see fig 1).

Quality assessment, study design, and sample characteristics

PEDro scores ranged from 5 to 9 out of 10 (table 2). Lower scores were mainly caused by lack of blinding of patients, therapists, or assessors and not conducting analyses with intention to treat when appropriate. Only 1 article[19] supplied a power calculation used to determine their sample size, but because of dropouts the results were subsequently underpowered. From the remaining studies, 6 highlighted their lack of power calculation[23-28] and 4 highlighted their small sample size[29-32] as methodologic limitations; 2 studies did not mention either a power calculation or comment on their sample size.[21,22,33]

From the studies included in the review, there were 9 randomized controlled trials (described in 11 articles),[19-22,24,25,27,29-31,33] 2 randomized trials,[26,28] and 2 randomized crossover trials.[23,32] The length of intervention ranged from 15 days to 24 weeks, and the frequency of intervention ranged from twice weekly to daily. Eight studies did not follow-up participants after the intervention period,[19-24,27-29,32,33] and 4 studies included a follow-up assessment at 4,[31] 8,[25] 10,[30] and 18 weeks[26] after the intervention had ended (table 3).

Six studies investigated physiotherapy as part of a multidimensional intervention,[21,22,26-28,30,33] and 7 studies investigated the use of only a physiotherapy intervention.[19,20,23-25,28,31,32] Study sample sizes ranged from 6 to 111 participants; EDSS scores ranged from 1.5 to 9.5. Eight studies included participants with both SPMS and PPMS,[21-24,27,31-33] and 5 studies included only participants with SPMS.[19,26,28-30] There were no studies that included only participants with PPMS (see table 3). There were 45 outcome measures used across the 15 articles, with few instances of commonality despite often measuring the same symptom or functional status. Baseline measurements of all outcome measures and final values or change values for the main findings of each study can be found in supplemental table S1 (available online only at http://www.archives-pmr.org/).

Interventions

There were 4 instances when the same type of intervention was implemented: physiotherapy as part of a multidisciplinary rehabilitation intervention was investigated by 2 studies,[21,22,33] functional electrical stimulation (FES) was investigated by

Table 1 Search strategies for electronic databases

Database	Search Strategy
Cochrane Library	(Progressive near/2 ("multiple sclerosis" or MS)) AND ((MeSH descriptor: [Physical Therapy Modalities] explode all trees) OR(MeSH descriptor: [Rehabilitation] explode all trees) OR (MeSH descriptor: [Exercise] explode all trees) OR (MeSH descriptor: [Resistance Training] explode all trees) OR (MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] explode all trees) OR (MeSH descriptor: [Electric Stimulation] explode all trees) OR(MeSH descriptor: [Acupuncture] explode all trees))
Web of Science Core Collections	((progressive NEAR/2 (MS OR "Multiple Sclerosis")) AND ((physiotherap* OR "physical therapy") OR (rehabilit*) OR (exercise OR training) OR ("electrical stimulation" OR FES OR NMES OR TENS OR "neuromuscular stimulation") OR (acupuncture)
Embase via Ovid	((progressive adj2 ("multiple sclerosis" or MS)).mp.) AND ((home physiotherapy OR physiotherapy) OR (prevention OR rehabilitation OR therapy OR rehabilit*.mp. OR rehabilitation center OR rehabilitation care OR breathing exercise OR muscle exercise OR arm exercise OR treadmill exercise OR aerobic exercise OR static exercise OR leg exercise OR isokinetic exercise OR closed kinetic chain exercise OR open kinetic chain exercise OR exercise.mp. OR exercise tolerance OR isometric exercise OR isotonic exercise OR aquatic exercise OR dynamic exercise OR stretching exercise OR anaerobic exercise OR exercise OR nerve stimulation OR electrostimulation therapy OR electroacupuncture OR functional electrical stimulation OR neuromuscular electrical stimulation OR transcutaneous nerve stimulation OR acupuncture OR acup.mp. electrostimulation OR functional electrical stimulation OR muscle OR gait)
MEDLINE via OVID	((progressive adj2 ("multiple sclerosis" or MS)).mp.) AND (exp Exercise Therapy physiotherapy.mp. OR physical therapy.mp. OR rehabilitation OR "activities of daily living" OR exercise therapy OR motion therapy, continuous passive OR muscle stretching exercises OR plyometric exercise OR resistance training OR rehabilitation, vocational OR exp Exercise Therapy OR exp Plyometric Exercise OR exercise.mp. OR exp Exercise Movement Techniques OR exp Exercise OR Electric Stimulation OR electric stimulation therapy OR electroacupuncture OR spinal cord stimulation OR transcutaneous electric nerve stimulation OR Transcutaneous Electric Nerve Stimulation OR exp Acupuncture Therapy OR exp Acupuncture Analgesia OR exp Acupuncture OR acupuncture.mp.)
PEDro	"progressive AND multiple AND sclerosis"

2 studies,[19,20,28] exercise therapy was investigated by 3 studies,[24,25,27] and a combination of botulinum toxin type A (BTX-A) injections and manual stretches was investigated by 2 studies.[26,30] The following interventions were investigated by 1 study each: acupuncture,[29] inspiratory muscle training,[31] body weight–supported treadmill training (BWSTT) and robotic orthotics,[32] and therapeutic standing using a standing frame.[23]

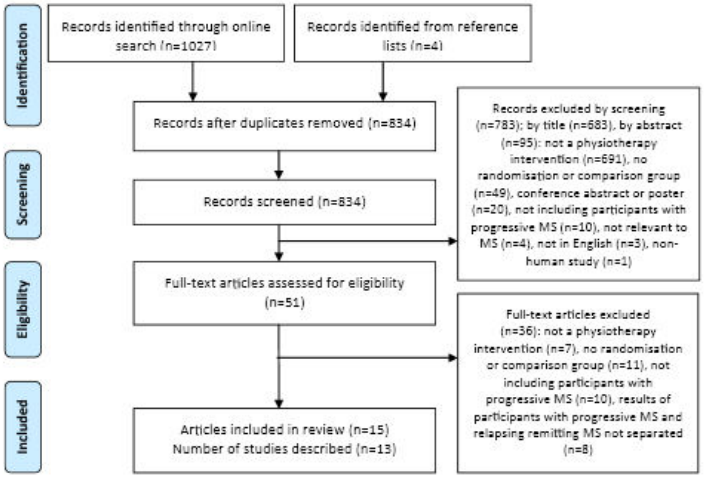

Fig 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of screening and inclusion process of included trials.

Table 2 PEDro scores for included studies

Author	Eligibility Criteria*	Random Allocation	Concealed Allocation	Baseline Comparability	Participant Blinding	Therapist Blinding	Assessor Blinding	<15% Dropout	Intention to Treat	Between-Group Difference	Point Estimate and Variability	Total (0–10)
Freeman et al[33]	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Patti et al[21,†]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Patti et al[22,†]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Kiefbeck and Hamrah Nedjad[31]	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Baker et al[23]	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	6
Giovannelli et al[30,‡]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Donnellan and Shanley[29]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Lo and Triche[32]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Barrett et al[19,§]	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5
Esnouf et al[20,§]	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Miller et al[25]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Paoloni et al[26]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Taylor et al[28]	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Briken et al[24]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Skjerbaek et al[27]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7

NOTE. E.C. assessed all articles,[19-33] L.P. assessed 8 articles,[19,20,23-26,32,33] and E.H.C. assessed 8 articles.[21,22,26-31]

Abbreviations: N, no; Y, yes.

* No point awarded for stating eligibility criteria.

† Patti et al[21,22] described the same study.

‡ All 3 reviewers rated this article initially and discussed results to ensure consistency.

§ Barrett,[19] Esnouf,[20] and colleagues described the same study.

Table 3 Evidence table

Author, Date, and Design	Sample Information	Intervention, Duration, Length of Session, and Frequency	Comparison/Control	Time Points (wk)	Outcome Measures*	Main Findings*
Freeman et al,[33] 1997, RCT	N=66 (PPMS: n=6; SPMS: n=60) EDSS range, 5.0–9.5 Dropout, n (%): 4 (6)	6wk, MDT inpatient rehabilitation, 45min, 2 times per week (n=32)	Wait-list control (n=34)	0, 6	Pri: EDSS, FIM, LHS	Between group: FIM ($P<.001$), LHS ($P<.01$)
Patti et al,[22] 2002, RCT	N=111 (PPMS: n=23; SPMS: n=88) EDSS range, 4–8 Dropout, n (%): 13 (12)	12wk: 6-wk MDT outpatient rehabilitation, 50–60min, 6 times per week, followed by 6wk HEP, 60min, 5 times per week (n=58)	HEP for 12wk (n=33)	0, 6, 12	Pri: EDSS, SF-36 Sec: BDI, SET, FIS	Between group: SF-36: RE subscale ($P<.005$), all other subscales ($P<.001$), BDI ($P<.001$), SET ($P<.001$), FIS ($P<.001$)
Patti et al,[21] 2003, RCT	N=111 (PPMS: n=23; SPMS n=88) EDSS range, 4–8 Dropout, n (%): 13 (12)	12wk: 6-wk MDT outpatient rehabilitation, 50–60min, 6 times per week, followed by 6wk HEP, 60min, 5 times per week (n=58)	HEP for 12wk (n=33)	0, 6, 12	Pri: FIM Sec: EDSS	Between group: FIM ($P<.001$)
Klefbeck and Hamrah Nedjad,[31] 2003, RCT	N=15 (all progressive MS) EDSS range, 6.5–9.5 Dropout, n (%): 1 (7)	10wk: inspiratory muscle trainer, 3 sets of 10 repetitions, twice every second day (n=7)	Normative treatment, which had deep breath exercises and regular phone calls (n=8)	0, 10, 14	Pri: VC, FVC, FVC%, FEV FEV%, Max insp pressure, Max exp pressure, FSS, Borg scale	Between group: Max insp pressure ($P<.01$) Within group: I: max exp pressure ($P<.02$)
Baker et al,[23] 2007, randomized crossover design	N=6 (all progressive MS) EDSS ≥7 Dropout, n (%): 0 (0)	3wk: standing frame, 30min/d (n=3) I and C swapped after 3wk (no washout period)	HEP of abdominal crunches, bridging, pelvic, and lumbar rolls, 5 repetitions of 8 exercises (n=3)	0, 3, 6	Pri: Ashworth Scale, spasm frequency, resting ROM in supine	Between group: Resting ROM in supine: L ankle ($P=.020$), R ankle ($P=.026$), L hip ($P=.039$), R hip ($P=.02$) Within group: I: Ashworth scale, R ankle ($P=.08$), L ankle ($P=.08$) C: spasm frequency, R leg ($P=.06$)
Giovannelli et al,[30] 2007, RCT	N=38 (all SPMS) EDSS range, 3–7.5 Dropout, n (%): 2 (5)	15d: I: BTX-A injection in either upper limb (FDS, FCU, FCR) or lower limb (tibialis posterior, gastrocnemius, soleus) followed by 40min/d of passive movements to prevent muscle contractures (n=20)	BTX-A injection only (n=28)	0, 2, 4, 12	Pri: MAS, VAS of relief from spasticity in injected muscle	Between group: MAS ($P<.01$), VAS ($P<.01$)
Donnellan and Shanley,[29] 2008, RCT	N=14 (all SPMS) EDSS range, 1.5–7.0 Dropout, n (%): 1 (7)	5wk: Chinese medical acupuncture, 2 times per week (n=7)	Minimal acupuncture†, 5wk, twice a week (n=7)	0, 5	Pri: MSIS-29 phys, MSIS-29 psych Sec: FSS, GHQ-12	Between group (C vs I): MSIS-29 psych subscore I ($P=.04$)

(*continued on next page*)

Table 3 (*continued*)

Author, Date, and Design	Sample Information	Intervention, Duration, Length of Session, and Frequency	Comparison/Control	Time Points (wk)	Outcome Measures*	Main Findings*
Lo and Triche,[32] 2008, randomized crossover design	N=13 (PPMS: n=5; SPMS: n=8) EDSS ± SD, 4.9±1.2 Dropout, n (%): 0 (0)	12wk: BWSTT, 3wk, 2 times per week, 40min, followed by 6wk washout then BWSTT as above and robot orthotics (n=6)†	Same as I but BWSTT and robot orthotics first (n=7)	0, 3, 9, 12	Pri: EDSS, timed 25-foot walk, 6-minute walk, DST Sec: step length ratio	Between group: DST: (P=.06) Within group: Whole sample: timed 25-foot walk (P=.0002), 6-min walk (P=.002), DST (P=.0007), EDSS (P=.001)
Barrett et al,[19] 2009, RCT	N=53 (all SPMS) EDSS range, 4–6.5 Drop out, n (%): 7 (13)	18wk, peroneal FES, worn in daily life (n=20)	HEP of trunk and pelvic stability and lower-limb strength, balance, and control exercises, 18wk, 1–2 times per day, 30min (n=24)	0, 6, 12, 18	Pri: 10-m walk speed Sec: 3-min walk distance	Within group: I with FES vs I without: 10-m walk speed (P=.001), 3-min walk distance (P=.004) C: 10-m walk speed (P=.001) C: 3-min walk distance (P=.005)
Esnouf et al,[20] 2010, RCT	N=64 (all SPMS) EDSS range, 4–6.5 Dropout, n (%): 11 (17)	18wk, peroneal FES, worn in daily life (n=32)	HEP of trunk and pelvic stability and lower-limb strength, balance, and control exercises, 18wk, 1–2 times per day, 30min (n=32)	0, 18	Pri: COPM performance and satisfaction scores, number of falls	Between group: COPM performance (P=.0038), satisfaction (P=.007) Falls (P=.036)
Miller et al,[25] 2011, RCT	N=30 (PPMS: n=11; SPMS: n=19) EDSS range, 6.5–8 Dropout, n (%): 2 (7)	8wk, domiciliary physiotherapy, 60min, 2 times per week (n=15)	Wait-list control (n=15)	0, 8, 16	Pri: MSIS-29 Sec: EDSS, FIM, MSQoL, MS-RS, BPI, HADA, HADD, dynamometry, 10-m walk, timed sit to stand	Between group: R knee extensor strength (P=.018), L knee flexor strength (P=.006), R knee flexor strength (P=.001), HADA (P=.014)
Paoloni et al,[26] 2013, RT (3-armed trial)	N=42 (all SPMS) EDSS range, 2–6 Dropout, n (%): 0 (0)	4wk: 3 times per week G1: 60min passive movements to prevent contractures plus 30min SMV (n=14) G2: BTX-A injection 2wk before study then same as G1 (n=14) G3: BTX-A injection 2wk before study and 60min passive movements same as G1 (n=14)	NA	0, 10, 22	Pri: MAS, FSS, Barthel index	Within group: G1: Knee MAS (P<.001), ankle MAS (P<.001), FSS (P=.004) G2: Knee MAS (P<.001), ankle MAS (P<.001), FSS (P=.05) G3: Knee MAS (P<.001), ankle MAS (P<.001) Both knee and ankle MAS higher at 22wk than 10wk (P<.05), FSS (P=.02), Barthel Index (P=.004)

(*continued on next page*)

Table 3 (*continued*)

Author, Date, and Design	Sample Information	Intervention, Duration, Length of Session, and Frequency	Comparison/Control	Time Points (wk)	Outcome Measures*	Main Findings*
Taylor et al,[28] 2014, RT	N=25 (all SPMS) EDSS range, 4—6.5 Dropout, n (%): 5 (20)	24wk: weeks 1—6: peroneal FES worn in daily life; weeks 7—12: addition of gluteal FES; weeks 13—18: 8 sessions of core stability physiotherapy and HEP of core stability exercises; weeks 19—24: continue with HEP FES wear continued for second 12wk (n=11)	Same as I but with physiotherapy and HEP first followed by FES (n=14)	−4, 0, 6, 12, 18, 24	Pri: ROGA, 10-m walk speed, MSIS-29, falls frequency	Between group: ROGA: without FES week 24 (P=.044), with FES week 18 (P=.028) Within group: I: MSIS-29 psych week 18 (P<.05), MSIS-29 phys week 24 (P<.05), 10-m walk speed with peroneal FES (P=.06) and gluteal FES (P=.06), falls frequency (P<.05) C: 10-m walk speed with FES vs no FES (P<.05), MSIS-29 phys week 24 (P<.05), falls frequency (P<.05)
Briken et al,[24] 2014, RCT (4-armed trial)	N=47 (PPMS: n=11; SPMS: n=31)§ EDSS range, 4—6 Dropout, n (%): 5 (11)	10wk, 15—45 min (Borg 2—3), 2—3 times per week 3 groups: arm ergometry (n=12), rowing (n=12), and cycling (n=12)†	Wait-list control n=11	0, 10	Pri: Vo_2peak, 6 Min walk, VLMT, IDS, FIS	Between group: Cycle group vs C: Vo_2peak (P=.003), 6-min walk test (P=.005), VLMT (P=.009), depression (P=.035) Arm group vs C: 6-min walk test (P=.003), VLMT (P=.007), fatigue (P=.013), IDS (P=.001) Rowing group vs C: VLMT (P=.001)
Skjerbaek et al,[27] 2014, RCT	N=11 (PPMS: n=3; SPMS: n=8) EDSS range, 6.5—8.0 Dropout, n (%): 1 (9)	4wk: 10 sessions, endurance training: predominantly UL exercises (6 x 3min at target heart rate [65%—75% HRmax]) and standard inpatient rehabilitation (n=6)	Standard inpatient rehabilitation (n=5)	0, 4	Pri: Vo_2peak, MDI, MSIS-29, 9HPT, HGT, BBT, 6minWCT	Between group: Vo_2peak (P=.06)

Abbreviations: BBT, Box and Block Test; BDI, Beck Depression Inventory; Borg, Borg rating of perceived exertion; BPI, Brief Pain Inventory; C, control group; COPM, Canadian Occupational Performance Measure; DST, double-limb support time; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDS, flexor digitorum superficialis, FEV, forced expiratory volume; FEV%, forced expiratory volume in percentage of forced vital capacity; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; FVC, forced vital capacity; FVC%, forced vital capacity percentage predicted; GHQ-12, General Health Questionnaire-12; G1, arm ergometry group; G2, rowing group; G3, cycling group; HADA, Hospital Anxiety and Depression Scale anxiety subscale; HADD, Hospital Anxiety and Depression Scale depression subscale; HEP, home exercise plan; HGT, hand grip test; HRmax, heart rate maximum; I, intervention group; IDS, Inventory of Depressive Symptoms; L, left; LHS, London Handicap Scale; MAS, Modified Ashworth Scale; Max exp, maximal expiratory; Max insp, maximal inspiratory; MDI, Major Depression Inventory; MDT, multidisciplinary team; Minimal acupuncture, a form of sham acupuncture where needles are inserted to a shallower depth and not at true acupuncture points (MacPherson et al[22]); MS-RS, multiple sclerosis-related symptom checklist; MSIS-29, Multiple Sclerosis Impact Scale; MSIS-29 phys, Multiple Sclerosis Impact Scale physical subscale; MSIS-29 psych, Multiple Sclerosis Impact Scale psychological subscale; MSQoL, Leeds Multiple Sclerosis Quality of Life Scale; NA, not applicable; 9HPGT, 9-Hole Peg Test; Pri, primary outcome measure; R, right; RCT, randomized controlled trial; RE, role functioning emotional subscale; ROGA, Rivermead observational gait analysis; ROM, range of motion; RT, randomized trial; Sec, secondary outcome measures; SET, Tempelaar Social Experience Checklist; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; 6minWCT, 6-minute wheelchair test; SMV, segmental muscle vibration; UL, upper limb; VAS, visual analog scale; VC, vital capacity; VLMT, Verbal Learning Memory Test; Vo_2peak, peak oxygen uptake.

* Baseline values of all outcome measures and final values/magnitude of changes can be found in supplemental table S1.

† Groups did not return to baseline after the 6-week washout period; therefore, analysis was conducted after the end of the first trial.

‡ Characteristic data of dropouts were not supplied.

Physiotherapy as part of a multidisciplinary rehabilitation program

The evidence is positive regarding the efficacy of a 6-week multidisciplinary rehabilitation program for the rehabilitation of people with progressive MS. The 2 studies (described in 3 articles) which used multidisciplinary rehabilitation programs found improvements in disability when measured using the FIM; however, the EDSS score remained unchanged.[21,22,33] Improvements were also found in depression, social experience, quality of life, and fatigue, and these were maintained at 6 weeks postintervention (see table 3).[21,22] The multidisciplinary rehabilitation programs differed both in delivery setting and control group interventions; however, both had positive effects.

FES

The evidence is conflicting regarding the efficacy of using FES as an intervention for the rehabilitation of people with progressive MS. The 2 studies which used FES (described in 3 articles) found positive results for an orthotic effect and decrease in falls with FES in comparison with a home exercise plan aimed at improving core stability.[19,20,28] However, Taylor et al[28] found their FES intervention produced a therapeutic effect in gait quality, whereas Barrett et al[19] found only their home exercise plan produced a therapeutic effect on walking speed and endurance. These conflicting results may be caused by differences in duration of the interventions, control group interventions, and use of gluteal stimulation in addition to peroneal FES by Taylor (see table 3).

Exercise therapy

The evidence is inconclusive regarding the efficacy of using exercise therapy for the rehabilitation of people with progressive MS. Two of the 3 studies that used exercise therapy investigated endurance training in a clinical environment,[24,27] and the third study investigated resistance training and functional exercises in a home environment.[25] The 2 endurance studies measured fitness and found improvements, but only Briken et al[24] reported a significant improvement.[27] Briken[24] also reported significant improvements in mobility, depression, fatigue, and cognitive function, and Miller et al[25] reported significant improvements in muscle strength and anxiety. There was no significant improvement in any of the other outcomes of these studies (see table 3). Differences in results between these studies may be caused by differences in inclusion criteria and the intervention protocol. Skjerbæk,[27] Miller,[25] and colleagues included participants with a higher level of disability (EDSS scores 6.5–8.0), whereas Briken[24] included participants with a moderate disability (EDSS scores 4–6). Skjerbæk,[27] Briken,[24] and colleagues conducted their final assessments at 4 and 6 weeks, respectively, without a follow-up assessment, whereas Miller[25] did a follow-up assessment 8 weeks after their 8-week intervention (see table 3).

BTX-A injections and manual stretches

The evidence in this review is positive regarding the efficacy of using a combination of BTX-A injections and manual stretches for the rehabilitation of people with progressive MS. However, it is unclear which combination is the most effective. The 2 studies that used BTX-A injections and manual stretches differed because Giovannelli et al[30] compared BTX-A injections with BTX-A injections and manual stretches, whereas Paoloni et al[26] conducted a 3-arm randomized trial investigating different combinations of BTX-A injections, manual stretches, and segmental muscle vibration (see table 3). Each group experienced improvements in spasticity, with those who only received BTX-A injections experiencing the least improvement.[30] Significant improvements were also found in subjective relief of symptoms,[30] fatigue, and activities of daily living[26] in those who received a combination of BTX-A injections and manual stretches; however, improvements in spasticity were not maintained at 18 weeks postintervention compared with 6 weeks postintervention.[26] In contrast, interventions incorporating segmental muscle vibration also produced significant improvements in spasticity; however, these improvements were maintained at follow-up assessments (see table 3).[26]

Acupuncture

The evidence is inconclusive regarding the efficacy of acupuncture for the rehabilitation of people with progressive MS. There was only 1 study that investigated Chinese medical acupuncture in comparison with minimal acupuncture[29] (a form of sham acupuncture where needles are inserted to a shallower depth and not at true acupuncture points[34]). Minimal acupuncture produced significant improvements in the psychological subscore of the Multiple Sclerosis Impact Scale compared with Chinese medical acupuncture. No changes were seen in any other outcomes (see table 3).

Inspiratory muscle training

The evidence in this review is positive regarding the efficacy of using inspiratory muscle training for the rehabilitation of people with progressive MS; however, only 1 study was found which investigated this technique. The study investigated the use of an inspiratory muscle trainer in comparison with deep breathing exercises.[31] A significant improvement was found in maximal inspiratory pressure and maximal expiratory pressure in those using the inspiratory muscle trainer. No changes were seen in any other outcomes (see table 3).

BWSTT and robotic orthotics

The evidence in this review is inconclusive regarding the efficacy of BWSTT and robotic orthotics for the rehabilitation of people with progressive MS. Only 1 study investigated BWSTT compared with BWSTT and robotic orthotics in a randomized crossover trial.[32] There was a trend toward improvement in double-limb support time in those receiving BWSTT compared with those receiving BWSTT and robotic orthotics. At the end of the study, all participants showed significant improvements in walking speed, endurance, double-limb support time, and disability but not in step length ratio (see table 3). However, after the washout period, values had not returned to baseline. Therefore, between-group analyses were performed after the initial 3-week intervention period.

Therapeutic standing

Similar to other physiotherapeutic interventions only 1 study investigated the efficacy of therapeutic standing for the rehabilitation of people with progressive MS. The use of a standing frame

was compared with a daily home exercise program consisting of abdominal crunches, hip rolls, lumbar rolls, and bridging.[23] Therapeutic standing produced significant improvements in passive hip and ankle range of motion and a trend toward improvement in ankle spasticity, whereas the home exercise program resulted in trends toward improvement in frequency of leg spasms (see table 3).

Overall outcome of studies

Generally, the articles presented a positive effect of physiotherapy for the rehabilitation of people with progressive MS. Thirteen studies (described in 15 articles) found that the intervention group improved more than the comparison or control group in at least 1 outcome measure.[19-25,27,30,31,33] One study only found statistically significant improvements in within-group analysis,[26] 1 study reported that neither group made an improvement large enough for statistical significance,[27] and 1 study found that participants who received the control treatment improved more than those who received the intervention.[29] Only 1 study used a power calculation to determine the required sample size; however, because of dropouts the results were subsequently underpowered.

Clinical significance of improvements

From the articles included in this review, where a statistically significant change in the outcome measure was reported, data detailing minimum clinically important differences (MCIDs) in people with MS were sought. Only 4 outcome measures had MCID data available: the timed 25-foot walk test (improvement of 17.2%),[35] the 6-minute walk test (improvement of 21.6m),[36] the Fatigue Impact Scale (improvement of 10–20 points),[37] and the physical subscore of the Multiple Sclerosis Impact Scale (improvement of 8 points).[38] Four studies had statistically significant results that used at least 1 of these outcome measures (table 4).[22,24,28,32] All of these results were above the level of the MCID for people with MS, indicating a positive perspective for using physiotherapy in the rehabilitation of people with progressive MS. The 4 trials used 4 different interventions: multidisciplinary rehabilitation,[22] FES,[28] exercise therapy,[24] and BWSTT and robotic orthotics.[32] Three trials included participants who were moderately affected by MS (EDSS scores 4–6.5),[24,28,32] and 1 study had a wider range and included those more severely affected (EDSS scores 4–8) (see table 4).[22] Two of the studies used the Fatigue Impact Scale,[22,24] and both produced similar levels of change despite Patti et al[22] including participants with a wider EDSS range and higher levels of fatigue at baseline. Similarly, 2 studies used the 6-minute walk test,[24,32] and both produced similar improvements despite differences in distance walked at baseline.

Discussion

Overall, the evidence presented in this review is positive regarding the efficacy of physiotherapy for the rehabilitation of people with progressive MS; however, the evidence is generally weak because of the variation in interventions and a lack of power within studies.

The International Progressive MS Alliance, and previous reviews, have highlighted that research regarding progressive MS and higher levels of disability is an area requiring further work.[5,13,15] Only 4 studies within the review included participants

Table 4 Statistically significant results of outcome measures with available data of MCIDs for people with MS

Author, EDSS range	Intervention	Outcome Measure (MCID)	Baseline Values	Change Values/Final Values
Patti et al,[22] 4–8	MDT outpatient rehabilitation	FIS (10–20 points)	I: 116.8±40.9 C: 127.0±36.0	I: −18.8±14.3† C: 0.6±0.9† (P<.001)‡
Taylor et al,[28] 4–6.5	FES	MSIS-29 physical subscore (8 points)	I: 48.8 (30.6–55.0) C: 46.3 (16.3–56.3)	I: 26.3 (16.2–38.1)§ (P<.05)‖ C: 35.0 (21.3–51.3)§ (P<.05)‖
Briken et al,[24] 4–6	Exercise therapy	6MWT (21.6m)	Cycling: 288.65±99.3m Arm: 296.79±123.79m Rowing: 306.61±103.69m C: 325.92±117.35m	Cycling: 344.97±118.30§ C: 319.49±109.49§ (P=.005)‡ Arm: 360.03±154.64§ C: 319.49±109.49§ (P=.003)‡
		FIS (10–20 points)	Cycling: 35.00±18.07 Arm: 45.00±14.73 Rowing: 35.27±13.86 C: 38.00±15.15	Arm: 31.80±11.09§ C: 39.30±17.49§ (P=.013)‡
Lo and Triche,[32] 4.9±1.2*	BWSTT and robot orthotics	T25fWT (17.2%)¶ 6MWT (21.6m)	Whole sample: 9.9±4.2s Whole sample: 220.3±96.5m	Whole sample: −3.1±2.4† (P=.0002)‖ Whole sample: 83.4±78.0† (P=.002)‖

NOTE. All baseline and change/final values are mean ± SD.

Abbreviations: Arm, arm ergometry group; C, control group; Cycling, cycling group; FIS, Fatigue Impact Scale (maximum score, 160); I, intervention group; MDT, multidisciplinary; MSIS-29, Multiple Sclerosis Impact Scale (maximal physical subscore, 80); 6MWT, 6-minute walk test; T25fWT, timed 25-foot walk test.

* Values are mean ± SD.

† Change values.

‡ Between-group analysis.

§ Final values.

‖ Within-group analysis.

¶ The 17.2% value is an improvement in change in speed.[35] Lo and Triche presented results in seconds.[32] Means of baseline and change in speed calculated from raw time data equated to a 40% improvement in speed.

with a high level of disability (EDSS score ≥6.5) (n=62), 5 studies did not make a distinction in the level of disability of their participants (n=242), and 4 studies included only participants with a mild to moderate level of disability (EDSS score ≤6) (n=178). Exercise therapy was the only intervention where the effects were compared across disability levels.[25,26,30] The results of these studies agreed with those of previously published reviews which found exercise therapy produced improvements in fatigue in those with a mild to moderate disability,[9] whereas no significant results were found in those with a higher level of disability.[6]

The results of this review were consistent with those found in systematic reviews of the other interventions for either MS or similar patient groups. Previously published reviews investigating the efficacy of physiotherapy interventions for people with MS found that multidisciplinary rehabilitation programs increased participation (as a result of a decrease in disability) and quality of life[39]; were unable to draw a conclusion as to the effectiveness of acupuncture[40]; found respiratory muscle trainers increased maximal inspiratory and expiratory pressure[41]; and found that BWSTT and BWSTT with robotic orthotics both improved walking speed, double-limb support time, endurance, and step length ratio.[42] However, there was no improvement in step length ratio in the study presented in this review. Two reviews assessing the efficacy of FES in chronic stroke found it had a good orthotic effect[43] but were unable to conclude on the efficacy of a therapeutic effect.[44] Reviews assessing interventions for neurologic impairments were unable to ascertain the most effective adjunct therapy to BTX-A injections in the treatment of spasticity[45] and that therapeutic standing produced improvements in ankle range of motion.[46] However, the similarity between the results of this review and other reviews for the same interventions in similar patient groups (eg, RRMS) should be approached with caution because of the previously mentioned methodologic weaknesses in the body of evidence presented.

Symptom management and rehabilitation is 1 of the 5 key research priorities identified by the International Progressive MS Alliance.[5] However, impact on quality of life and participation should also be a consideration. Therefore, identifying the patient groups who would experience the greatest improvement in clinical outcomes to particular interventions, with the greatest impact on quality of life and participation, would help establish the full effectiveness of the interventions.

Study limitations

This review was limited to only include articles published in English. It was further limited by the broad spectrum of physiotherapy as a discipline, which led to variation in duration, dose, intensity, and type of interventions included.

Future work

We recommend future work should be carried out to investigate physiotherapy interventions for people with progressive MS using adequately powered randomized trials with an appropriate control, long-term follow-up, and adequate reporting.[47] Studies should, where possible, aim to use a core set of outcome measures[48] and use outcome measures for which there are available data of MCID for people with MS. Future research should also consider participants with PPMS and SPMS separately to investigate whether this has an effect on clinical outcomes. We also recommend investigation to ascertain which patient groups would experience the largest improvements in quality of life from improvements in clinical outcomes.

Conclusions

The evidence within this review demonstrates that physiotherapy may be effective in the rehabilitation of people with progressive MS. This review, which focused on people with progressive MS, had similar findings to reviews in similar patient groups. Further investigation, with appropriately powered studies and consistency in outcome measures between studies, is required to strengthen this evidence base and conduct meta-analyses of the evidence.

Keywords

Exercise; Multiple sclerosis; Physical therapy modalities; Rehabilitation; Review [publication type]

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Supplemental Table S1 Primary and secondary outcome measures with baseline values and main findings from each trial

Author, Date, and Design	Outcome Measures and Baseline Values	Main Findings: Intervention, Control
Freeman et al,[33] 1997, RCT	Pri: EDSS*: I: 6.5 (5.0—9.0), C: 6.5(6.0—8.5) FIM*: I: 67 (13—87), C: 69.5 (18—84) LHS: I: 61.5±13, C: 66.2±8.74	Between group (change values): FIM*: motor domain: 4.0(−10 to 19), 2.5 (−16 to 5) (P<.001), self-care domain: 1.5 (−5 to 9), −1.0 (−9 to 3) (P<.0001) LHS: 2.9±8.9, −2.7±8.6 (P<0.01)
Patti et al,[22] 2002, RCT	Pri: EDSS: I: 6.2±1.2, C: 6.1±1.2 SF-36 subscales RE: I: 56.1±40.4, C: 42.1±43.4 PF: I: 39.3±23.0, C: 31.2±23.1 RP: I: 36.9±36.2, C: 26.4±36.8 BP: I: 58.2±26.0, C: 65.4±27.1 GH: I: 49.9±21.1, C: 45.0±20.6 VT: I: 47.8±17.5, C: 42.7±18.4 SF: I: 59.8±21.5, C: 57.6±27.1 MH: I: 54.2±22.8, C: 53.4±23.7 Sec: BDI: I: 11.0±7.5, C: 12.5±7.6 SET: I: 28.9±6.0, C: 29.3±5.9 FIS: I: 116.8±40.9, C: 127.0±36.0	Between group (change values): SF-36 subscales: RE: 6.2±23.7, −0.1±0.3 (P<.005) PF: 6.91±18.1, −0.1±0.3 (P<.001) RP: 14±24.3, −0.2±0.5 (P<.001) BP: 14.9±20.0, −0.1±0.6 (P<.001) GH: 5.8±10.5, −0.2±0.5 (P<.001) VT: 7.4±12.5, −0.1±0.5 (P<.001) SF: 11.5±14.6, −0.1±0.3 (P<.001) MH: 7.7±15.8, −0.1±0.5 (P<.001) BDI: −2.2±3.4, 0.1±1.0 (P<.001) SET: −2.6±6.0, −0.3±0.8 (P<.001) FIS: −18.8±14.3, 0.6±0.9 (P<.001)
Patti et al,[21] 2003, RCT	Pri: FIM: I: 92.9±11.0, C: 93.7±16.4 Sec: EDSS: I: 6.2±1.2, C: 6.1±1.2	Between group (change values): FIM: 10.2±11.8, 0.0±0.7 (P<.001)
Klefbeck and Hamrah Nedjad,[31] 2003, RCT	Pri: VC (liter)*: I: 2.4 (0.5—3.4), C: 2.1 (0.5—6.2) FVC (liter)*: I: 2.7 (1.0—3.4), C: 2.6 (1.3—6.7) FVC%*: I: 78 (36—93), C: 69 (38—127) FEV (liter)*: I: 2.2 (1.0—3.3), C: 2.3 (1.3—5.0) FEV%*: I: 83 (82—100), C: 88 (81—100) Max insp pressure (cmH_20)*: I: 42 (28—74), C: 52 (15—120) Max exp pressure (cmH_20)*: I: 46 (36—58), C: 51 (20—147) FSS*: I: 4.2 (2.8—6.0), C: 5.1 (2.0—6.7) Borg scale*: I: 14 (9—17), C: 14 (10—17)	Between group (final values): Max insp pressure*: 67 (55—100),C: 54 (10—126) (P<.01) Within group (final values): I: max exp pressure*: 63 (44—80) (P<.02)
Baker et al,[23] 2007, randomised crossover design	Pri: Ashworth Scale*: whole sample: R hip flex: 1.5 (1—3), L hip flex: 2.0 (1—2), R hip abd: 1.0 (1—3), L hip abd: 2.0 (1—2), R knee: 1.5 (2—3), L knee: 2.0 (2—3), R ankle: 2.0 (2—3), L ankle: 2.0 (2—3) Spasm frequency*: whole sample: R: I: 2.0 (0—4), L: I: 2.0 (0—4) Resting ROM in supine*: whole sample: R ankle: 10 (10—12), L ankle: 13.5 (10—15), R knee: 2.5 (0—5), L knee: 2.0 (0—2), R hip: 10 (0—10), L hip: 20 (5—20)	Between group (final values): Resting ROM in supine*: R ankle: 5.0 (−5 to 7), 10 (7—12) (P=.02) L ankle: 2.5 (0—7), 10 (10—15) (P=.026) R hip: 0.0 (0—5), 10 (5—15) (P=.02) L hip: 5.0 (0—10), 10 (5—10) (P=.039) Within group (final values): I: Ashworth scale*: R ankle: 2.0 (1—3) (P=.08) L ankle: 1.5 (1—3) (P=.08) C: spasm frequency R leg*: 1.0 (0—4) (P=.06)
Giovannelli et al,[30] 2007, RCT	Pri: MAS: I: 3.63±0.49, C: 3.61±0.50 VAS of relief from spasticity in injected muscle, week 2: I: 5.18±1.10, C: 5.50±1.38	Between group (change values): MAS: −0.95±0.78, −0.28±0.46 (P<.01) VAS of relief from spasticity in injected muscle: 2.68±1.08, 1.06±1.16 (P<.01)
Donnellan and Shanley,[29] 2008, RCT	Pri: MSIS-29 phys: I: 55.2±23.6, C: 57.7±23.8 MSIS-29 psych: I: 34.3±23.7, C: 48.4±30.0 Sec: FSS: I: 4.6±2.4, C: 2.8±1.9 GHQ-12: I: 15.8±9.9, C: 17.7±9.5	Between group (change values, C vs I): MSIS-29 psych: 23±21.0, 6.0±13.9 (P=.04)
Lo and Triche,[32] 2008, randomised crossover design	Pri: EDSS: whole sample: 4.9±1.2 25-foot walk (s): whole sample: 9.9±4.2 6MWT (m): whole sample: 220.3±96.5 DST (%): whole sample: 33.2±8.0 Sec: step length ratio: whole sample: 0.9±0.1	Between group (change values): DST: −7.1±3.9, −1.7±3.9 (P=.06) Within group (change values): 25-foot walk: 3.1±2.4 (P=.0002) 6MWT: 83.4±78.0 (P=.002) DST: −5.5±4.1 (P=.0007) EDSS: −1.0±0.7 (P=.001)

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Supplemental Table S1 (*continued*)

Author, Date, and Design	Outcome Measures and Baseline Values	Main Findings: Intervention, Control
Barrett et al,[19] 2009, RCT	Pri: 10-m walk (ms^{-1}): I: 0.79±0.35, C: 0.68±0.28 Sec: 3-min walk (m): I: 99±44, C: 97±44	Within group (final values): I with FES vs I without: 10-m walk: 0.80±0.35 ($P=.001$) 3-min walk: 125±55 ($P=.004$) C: 10-m walk: 0.77±0.29 ($P=.001$) C: 3-min walk: 113±46 ($P=.005$)
Esnouf et al,[20] 2010, RCT	Pri: COPM performance*: I: 3.5 (1.75–5.0), C: 3.4 (2.2–5.6) COPM satisfaction*: I: 2.2 (1.0–5.0), C: 2.6 (1.0–4.6) No. of falls: N/A	Between group (change values): COPM performance*: 1.1 (0.1–2.0), 0.0 (0.0–0.9) ($P=.0038$) COPM satisfaction*: 1.7 (0.3–2.7), 0.0 (0.0–1.0) ($P=.007$) No. of falls (final values)*: 5, 18 ($P=.036$)
Miller et al,[25] 2011, RCT	Pri: MSIS-29: I: 89.9±22.8, C: 82.8±17.3 Sec: EDSS: I: 7±0.5, C: 7.1±8.1 FIM: I: 68.9±12.9, C: 72.2±14.2 MSQoL: I: 11.9±5.3, C: 8.3±5.3 MS-RS: I: 32.7±13.9, C: 27.9±9.4 BPI: I: 26.7±27.7, C: 25.6±17.7 HADA: I: 6.0±5.7, C: 3.1±2.1 HADD: I: 5.8±3.3, C: 6.3±3.6 Dynamometry (kg): R knee ext: I: 10.0±5.9, C: 9.3±6.0, R knee flex: I: 9.7±5.1, C: 5.5±4.3, L knee ext: I: 7.2±5.1, C: 8.4±6.7, L knee flex: I: 7.7±6.0, C: 7.5±6.8 10-m walk (s): I: 41.2±32.9, C: 43.4±27.7 Timed sit to stand (s): I: 6.2±2.3, C: 5.8±3.4	Between group (change values): R knee ext strength: 11.1±6.1, 8.4±6.7 ($P=.018$) L knee flexor strength: 6.9±5.3, 5.0±5.6 ($P=.006$) R knee flexor strength: 8.7±5.7, 4.8±4.2 ($P=.001$) HADA: 6.2±5.0, 3.8±4.0 ($P=.014$)
Paolini et al,[26] 2013, randomized trial (3-armed trial)	Pri: Knee MAS†: G1: 3 (3–4), G2: 4 (3–4), G3: 4 (3–4) Ankle MAS†: G1: 4 (3–4), G2: 4 (4–4), G3: 4 (4–4) FSS‡: G1: 53.6±2.31, G2: 43.4±3.10, G3: 48.5±2.77 Barthel Index‡: G1: 79.8±1.63, G2: 76.4±2.95, G3: 77.5±1.50	Within group (final values): G1: Knee MAS†: 3 (2–3) ($P<.001$) Ankle MAS†: 3 (2–3) ($P<.001$) FSS‡: 46.7±2.75 ($P=.004$) G2: Knee MAS†: 3 (2–3) ($P<.001$) Ankle MAS†: 3 (3–4) ($P<.001$) FSS‡: 39.7±2.97 ($P=.05$) G3: Knee MAS†: 3 (2–4) ($P<.001$) Ankle MAS†: 4 (3–4) ($P<.001$) Knee and ankle MAS higher at 22wk than 10wk: week 10 values: knee MAS†: 3 (2–3) ($P<.05$), ankle MAS: 3 (3–4) ($P<.05$) FSS‡: 42.5±2.17 ($P=.02$) Barthel Index‡: 77.8±1.47 ($P=.004$)
Taylor et al,[28] 2014, randomized trial	Pri: ROGA without FES†: I: 13.0 (8.5–21), C: 15 (11.5–17.5) 10-m walk (ms^{-1})†: I: 0.72 (0.47–1.31), C: 0.82 (0.51–1.01) MSIS-29 phys†: I: 48.8 (30.6–55.0), C: 46.3 (16.3–56.3) MSIS-29 psych†: I: 38.8 (23.6–54.2), C: 27.2 (11.1–50.0) Falls frequency†: I: 23.3 (8.3–67.1), C: 9.75 (1.1–50.0)	Between group (final values): ROGA†: without FES week 24: 11 (6–14.3), 17 (14.5–20) ($P=.044$), with FES week 18: 10 (5.3–13), 12 (10–16) ($P=.028$) Within group (final values): I: MSIS-29 phys†: 26.3 (16.2–38.1) ($P<.05$), MSIS-29 psych†: week 18: 19.4 (9.7–27.3) ($P<.05$) 10-m walk†: with peroneal FES: 1.2 (0.72–1.27) ($P=.06$), with peroneal and gluteal FES‡: 1.04 (0.76–1.27) ($P=.06$) Falls frequency†: 4 (3.0–7.75) ($P<.05$) C: 10-m walk with peroneal and gluteal FES vs no FES†: 0.89 (0.64–1.09) ($P<.05$) MSIS-29 phys†: 35.0 (21.3–51.3) ($P<.05$) Falls frequency†: 0.5 (0.0–3.075) ($P<.05$)

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Supplemental Table S1 (*continued*)

Author, Date, and Design	Outcome Measures and Baseline Values	Main Findings: Intervention, Control
Briken et al,[24] 2014, RCT (4-armed trial)	Pri: Vo_2peak ($ml \cdot O_2 \cdot min^{-1}$): cycling: 1490.18±528.20, arm ergometry: 1352.30±431.26, rowing: 1306.00±421.79, C: 1377.40±325.19 Sec: 6MWT (m): cycling: 288.65±99.3, arm ergometry: 296.79±123.79, rowing: 306.61±103.69, C: 325.92±117.35 VLMT: cycling: 52.18±6.03, arm ergometry: 46.80±10.22, rowing: 51.09±10.42, C: 47.50±5.91 IDS: cycling: 18.36±12.27, arm ergometry: 21.10±10.24, rowing: 13.91±7.82, C: 14.10±7.94, FIS†: cycling: 35.00±18.07, arm ergometry: 45.00±14.73, rowing: 35.27±13.86, C: 38.00(15.15)	Between group (final values): Cycling vs C: Vo_2peak: 1253.70±297.33 ($P=.003$) 6MWT: 344.97±118.30, 319.49±109.49 ($P=.005$) VLMT: 62.00±7.18, 51.50±8.20 ($P=.009$) IDS: 14.73±9.49, 18.40±10.36 ($P=.035$) Arm ergometry vs C: 6MWT: 360.03±154.64, 319.49±109.49 ($P=.003$) VLMT: 58.10±8.48, 51.50±8.20 ($P=.007$), FIS: 31.80±11.09, 39.30±17.49 ($P=.013$), IDS: 12.30±6.57, 18.40±10.36) ($P=.001$) Rowing vs C: VLMT: 63.09±9.94, 51.50±8.20 ($P=.001$)
Skjerbaek et al,[27] 2014, RCT	Pri: Vo_2peak ($ml \cdot O_2 \cdot min^{-1}$): I: 642±209, C: 872±386 MDI: I: 10.6±1.7, C: 14.6±7.3 MSIS-29: I: 86±11.9, C: 76±20.5 9HPGT (s): I: 36.8±13.6, C: 66.9±61.7 HGT (N): I: 20.3±8.7, C: 19.9±10.3 BBT ($blocks \cdot min^{-1}$): I: 23.6±8.5, C: 27.0±8.4 6minWCT (m): I: 205±136, C: 313±71	Between group (change values): Vo_2peak: 308±312, 2±29 ($P=.06$)

NOTE. Values are mean ± SD or as otherwise indicated.

Abbreviations: abd, abduction; BBT, Box and Block Test; BDI, Beck Depression Inventory; Borg, Borg rating of perceived exertion; BP, bodily pain; BPI, Brief Pain Inventory; C, control group; COPM, Canadian Occupational Performance Measure; DST, double-limb support time; ext, extensor; FEV, forced expiratory volume; FEV%, forced expiratory volume in percentage of forced vital capacity; FIS, Fatigue Impact Scale; flex, flexion; FSS, Fatigue Severity Scale; FVC, forced vital capacity; FVC%, forced vital capacity percentage predicted; G1, group 1; G2, group 2; G3, group 3; GH, general health; GHQ-12, General Health Questionnaire-12; HADA, Hospital Anxiety and Depression Scale anxiety subscale; HADD, Hospital Anxiety and Depression Scale depression subscale; HGT, hand grip test; I, intervention group; IDS, Inventory of Depressive Symptoms; L, left; LHS, London Handicap Scale; MAS, Modified Ashworth Scale; Max exp, maximal expiratory; Max insp, maximal inspiratory; MDI, Major Depression Inventory; MH, mental health; MS-RS, multiple sclerosis-related symptom checklist; MSIS-29, Multiple Sclerosis Impact Scale; MSIS-29 phys, Multiple Sclerosis Impact Scale physical subscale; MSIS-29 psych, Multiple Sclerosis Impact Scale psychological subscale; MSQoL, Leeds Multiple Sclerosis Quality of Life Scale; N/A, not applicable; 9HPGT, 9-Hole Peg Test; PF, physical functioning; Pri, primary outcome measure; R, right; RCT, randomized controlled trial; RE, role functioning emotional; ROGA, Rivermead observational gait analysis; ROM, range of motion; RP, role physical; Sec, secondary outcome measures; SET, Tempelaar Social Experience Checklist; SF, social functioning; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; 6minWCT, 6-minute wheelchair test; 6MWT, 6-minute walk test; VAS, visual analog scale; VC, vital capacity; VLMT, Verbal Learning Memory Test; Vo_2peak, peak oxygen uptake; VT, vitality.

* Values are median (range).

† Values are median (interquartile range).

‡ Values are mean ± SE.

Appendix 2 – Access delivery and perceived efficacy of physiotherapy and use of complementary and alternative therapies by people with progressive multiple sclerosis in the United Kingdom: An online survey

Multiple Sclerosis and Related Disorders 12 (2017) 64–69

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Access, delivery and perceived efficacy of physiotherapy and use of complementary and alternative therapies by people with progressive multiple sclerosis in the United Kingdom: An online survey

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ARTICLE INFO

Keywords:
Progressive multiple sclerosis
Physiotherapy
Access
Rehabilitation
Complementary therapies

ABSTRACT

Introduction: All people with progressive MS in the United Kingdom should have access to physiotherapy through the National Health Service (NHS). However levels of access and delivery are unknown. Furthermore there is no research on perceived efficacy of physiotherapy or the use of complementary and alternative medicine in people with progressive MS in the United Kingdom.

Methods: An online survey was carried out via the UK MS Register. Inclusion criteria were diagnosis of progressive MS, a member of UK MS Register and 18 years or older. The survey asked participants regarding access and delivery of physiotherapy; perceived efficacy of physiotherapy and interventions received; barriers to accessing physiotherapy and use of complementary and alternative medicine. The following additional data were supplied from the UK MS Register: demographics, EQ5D, MSIS-29 physical and psychological sub-scales and geographical data.

Results: Total number of respondents was 1,298 from an identified 2,538 potential registrants: 87% could access physiotherapy services, 77% received physiotherapy from the NHS and 32% were currently receiving physiotherapy. The most common interventions received were home exercise programme (86%), exercises with a physiotherapist (74%) and advice/education (67%). 40% had recently used complementary and alternative medicine.

Perceived efficacy of physiotherapy was high with 70% reporting it to be either 'beneficial' or 'very beneficial'. Main barriers to accessing physiotherapy were mobility, fatigue, continence, transport issues, requiring someone to go with them and pain.

Discussion: Access to physiotherapy was high with most people reporting it as beneficial. However 13% reported not having access indicating a gap in accessibility. Considering some of the barriers reported may allow physiotherapy services to address this gap in accessibility.

1. Introduction

In the United Kingdom there are an estimated 130,000 people living with multiple sclerosis (Mackenzie et al., 2014). Approximately 15% of new cases are diagnosed as primary progressive multiple sclerosis, 5% as progressive relapsing multiple sclerosis and 80% as relapsing remitting multiple sclerosis. Around two thirds of those with relapsing remitting multiple sclerosis will however, go on to develop secondary progressive multiple sclerosis (Miller and Leary, 2007). Due to the lack of pharmacological treatments for decreasing disease activity in those with progressive forms of multiple sclerosis, treatment often focuses on symptomatic management and rehabilitation. To that

Abbreviations: EQ-5D-3L, EQ-5D-3L Health Questionnaire; MS, multiple sclerosis; MSIS-29, Multiple Sclerosis Impact Scale version 2; NHS, National Health Service; SD, Standard Deviation

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http://dx.doi.org/10.1016/j.msard.2017.01.002
Received 7 November 2016; Received in revised form 16 December 2016; Accepted 4 January 2017

effect, the International Progressive MS Alliance has named rehabilitation of as one of its research priorities for progressive multiple sclerosis (Fox et al., 2012).

For people with progressive multiple sclerosis in the United Kingdom, access to physiotherapy via the National Health Service is recommended in guidelines produced by the National Institute for Health and Care Excellence (NICE, 2014) and is part of the Healthcare Improvement Scotland neurological clinical standards (Healthcare Improvement Scotland, 2009). However, poor patient satisfaction with access to multiple sclerosis physiotherapy services has been reported in several areas of the United Kingdom (Edmonds et al., 2007; MacLurg et al., 2005; Markwick et al., 2014). In the Republic of Ireland, access to physiotherapy is reportedly lower in those from rural areas and in people with progressive multiple sclerosis compared to people with relapsing remitting multiple sclerosis (Lonergan et al., 2015). In addition, high levels of patient satisfaction with physiotherapy services have been reported in Sweden and Norway (Normann et al., 2012; Ytterberg et al., 2008).

Despite previous studies highlighting dissatisfaction with physiotherapy services in different parts of the United Kingdom the access, and use of physiotherapy services specifically by people with progressive multiple sclerosis across the whole of the United Kingdom is unknown. Furthermore, the perceived efficacy of physiotherapy services and barriers to accessing them is also unknown. In addition to traditional clinical services, people with multiple sclerosis often utilise complementary and alternative therapies in the management of their condition and whilst there is literature examining usage across the Nordic countries (46–58%) (Skovgaard et al., 2012), the United States of America (58%) (Stoll et al., 2012), Germany (67%) (Apel et al., 2006), and Turkey (26%) (Gedizlioglu et al., 2015) there is currently no information on the use of complementary and alternative therapies by people with progressive multiple sclerosis in the United Kingdom.

The objectives of this study were to: investigate access, use, delivery and perceived efficacy of physiotherapy services and interventions; determine barriers to accessing physiotherapy services; and assess use of complementary and alternative therapies by people with progressive multiple sclerosis in the United Kingdom.

2. Methods

2.1. Design and participant recruitment

In this cross-sectional study an online survey was carried out with participants on the UK MS Register. Registrants sign up voluntarily to the UK MS Register and provide self-reported demographic information and diagnosis of multiple sclerosis (Ford et al., 2012). Registrants answer targeted surveys and complete regular self-report measures such as the EQ-5D-3L Health Questionnaire (EQ-5D-3L) and the Multiple Sclerosis Impact Scale version 2 (MSIS-29) (described below). Participant's data are anonymised and researchers are given secure access to the data remotely via the Secure Anonymised Information Linkage gateway (Jones et al., 2014). At the time of this study the UK MS Register had 11,041 members with 4,384 being active on the Register in the 6 months prior. In total there were 2,538 registrants who reported having a progressive form of multiple sclerosis.

Participants were eligible for inclusion to this study if they were members of the UK MS Register, aged 18 years or older, and had a progressive form of multiple sclerosis. Participants were identified by the UK MS Register and emailed informing them of the survey. The survey was conducted between August and October 2015. Informed consent was assumed if a participant completed the survey.

2.2. Data collection

The survey comprised two sections. The first contained questions related to access, delivery, perceived efficacy of physiotherapy and use of complementary and alternative therapies. The second was concerned with access to and use of multiple sclerosis specialist and clinical services. Only the first section is described here. The survey took approximately 40 min to complete and a copy is available upon request.

The first section asked respondents regarding access to physiotherapy; if they currently received physiotherapy for their multiple sclerosis; the referral process; their physiotherapy provider; their perceived efficacy of physiotherapy; the frequency and duration of appointments; waiting times for appointments; how and where they received physiotherapy; and barriers to receiving physiotherapy. Those who were currently receiving physiotherapy were asked what physiotherapy interventions they had received in the prior three months and their perceived efficacy of these. Finally participants were asked which complementary and alternative therapies they had used in the prior three months. As acupuncture is delivered as a physiotherapy intervention and as a complementary and alternative therapy it was included in both questions. Questions were closed and participants were able to select answers from a list of options. In some questions participants were able to choose more than one answer. Perceived efficacy was rated on a five point scale as: 'very harmful', 'harmful', 'neither harmful nor beneficial', 'beneficial', and 'very beneficial'.

2.3. Additional data

The UK MS Register provided the following additional data: demographics; time since diagnosis; Lower Super Output Area codes for participants in England and Wales; Super Output Area codes for participants in Scotland (there were no geographical codes available for participants in Northern Ireland). The Lower Super Output Area and Super Output Area codes were converted into a classification of rural and urban living using available conversion data (Office for National Statistics, 2016; Scottish Office for National Statistics, 2016). Urban living was defined as a settlement of 10,000 people or more (Department for Communities and Local Govenment, 2006). The results from the most recent EQ-5D-3L and MSIS-29 questionnaires completed by participants were also provided. The EQ-5D-3L is a self-report measure of quality of life which generates an index ranging from −1 to 1 with a higher index indicating a higher quality of life and an index less than zero indicating a quality of life worse than death (EuroQol, 1990). The MSIS-29 version 2 is a self-report measure which considers the physical and psychological impact of multiple sclerosis in two sub-scales ranging from 20 to 80 and 7 to 36 respectively. A higher score indicates a greater impact of multiple sclerosis (Hobart et al., 2001).

2.4. Ethical approval

Ethical approval was granted by the University of Glasgow's College of Medical, Veterinary & Life Sciences Ethics Committee and the study was peer reviewed by the information governance panel of the UK MS Register (South West - Central Bristol Research Ethics Committee, Ref: 11/SW/0160).

2.5. Statistics

Data were analysed using IBM SPSS v22. All variables were characterised using descriptive statistics. Where appropriate variables were checked for normality, since data were not normally distributed Mann-Whitney, Kruskal-Wallis and chi square tests were used as appropriate. Statistical significance was set at $p < 0.05$. Where results are presented as a percentage the total number of responses for that question is reported in brackets.

3. Results

In total 2538 people were identified from the UK MS register as

Table 1
Characteristics of survey responders.

Number of participants	1298
Age (years)	59 SD 8
Time since diagnosis (years)	16 SD 9
Gender	
Female	824
Male	474
Country	
Scotland	131
England	1029
Wales	104
N. Ireland	21
EQ-5D-3L index	0.49 SD 0.20
MSIS-29 –psychological sub-scale	19.96 SD 6.10
MSIS-29 – physical sub-scale	55.97 SD 12.64

Figures where applicable are mean (standard deviation (SD)). Not all participants provided geographical information. The mean time between completion of the survey and the most recent EQ-5D-3L and MSIS-29 was 39 (SD 120) and 19 (SD 111) days respectively.
EQ-5D-3L: EQ-5D-3L Health Questionnaire

potential participants and were emailed with a link to take part in the survey. Of those, 1298 completed the survey producing a response rate of 51% (Table 1).

Of the respondents, 87% (n=1118) had access to physiotherapy and 32% (n=414) were currently receiving physiotherapy for their multiple sclerosis (Table 2). The most common methods of referral to physiotherapy were via a multiple sclerosis specialist nurse (43%) and self-referral (38%). Approximately three quarter of participants were receiving their physiotherapy from the National Health Service and the remainder from private providers or charitable organisations. Seventy one percent received their physiotherapy at home (25%) or in a clinical environment or hospital (46%). The majority of people (80%) reported they received physiotherapy on a one to one basis. Ninety percent estimated a waiting time of 12 weeks or less after referral and over half of respondents received their physiotherapy once per week or more frequently (Table 2).

In total 70% of respondents thought that physiotherapy was either 'beneficial' or 'very beneficial' for their multiple sclerosis, 27% were indifferent in their opinion and 3% thought that physiotherapy was 'harmful' or 'very harmful'. The perceived efficacy of physiotherapy was higher among those who were currently receiving physiotherapy for their multiple sclerosis than those who were not ($p < 0.001$) (Fig. 1). Only eight of the 31 participants with a negative opinion of physiotherapy had actually received a physiotherapy intervention in the prior three months (independent exercise (n=4), exercise with a physiotherapist (n=2) and advice/education (n=2)).

The most commonly received physiotherapy interventions were; home exercise programme (86%); exercises with a physiotherapist (74%) and advice or education (67%). The perceived efficacy of all interventions was predominantly 'beneficial' or 'very beneficial'. People who received acupuncture and transcutaneous electrical nerve stimulation were less positive about the efficacy of these interventions although the opinion of these interventions was still predominantly positive (Table 3). Statistical analysis was not possible due to the small proportions of participants who felt that physiotherapy would be harmful to them.

Eighty nine percent of those receiving their physiotherapy from non- National Health Service providers had an expected waiting time of four weeks or less for a physiotherapy appointment compared to 39% of those receiving National Health Service physiotherapy (Table 4).

The most common barriers to receiving physiotherapy were described as: mobility (40%), fatigue (39%), continence issues (21%), transport issues (21%), and needing someone to go with them (21%). Participants were also asked to identify the three greatest barriers to

Table 2
Access, referral, and delivery of physiotherapy.

Question	Answers	n	%
Can you get physiotherapy if you want it?n=1291	yes	1118	87
	no	173	13
Are you currently receiving physiotherapy for your MS? n=1287	yes	414	32
	no	873	68
Who would you speak to get a physiotherapy appointment? n=1158	MS specialist doctor/ neurologist	310	27
	GP	366	32
	I self-refer	445	38
	MS specialist nurse	493	43
	Other	140	12
	Don't know	8	1
Who provides your physiotherapy? n=1106	National Health Service	855	77
	Private (self-funded)	207	19
	Private (insurance)	21	2
	Charity	173	16
	Other	58	5
Where do you usually receive physiotherapy?n=461	In a hospital or clinic	210	46
	At home	116	25
	In a charity centre	110	24
	In a community centre	31	7
	[a]Other	63	14
How many patients are normally present at your physiotherapy sessions?n=457	1 (individual session)	366	80
	2–4	42	9
	5 or more	81	18
	I receive physiotherapy by telephone or online	5	1
What is your usual pattern of appointments?n=451	Regularly	270	60
	Varies depending on symptoms	181	40
How long would you expect to wait for a physiotherapy appointment? n=192	< 1 week	12	6
	1 or more but less than 2 weeks	42	22
	2 or more but less than 4 weeks	36	19
	4 or more but less than 6 weeks	41	21
	6 or more less than 12 weeks	41	21
	> 12 weeks	20	10
How often do you usually receive physiotherapy?n=252	once or more a week	138	55
	once a fortnight	46	18
	once every 1–3 months	53	21
	twice a year	10	4
	once a year or less	5	2
What is the usual length of your physiotherapy sessions?n=462	< 30 min	120	26
	30–60 min	299	65
	> 60 min	43	9

For some questions participants were able to select more than one option.
MS: multiple sclerosis; n: number of responses.
[a] Setting of delivery named as 'other' included: care home; private clinic; hydrotherapy pool; charity centre; leisure centre/gym.

receiving physiotherapy and pain was named as a barrier in addition to those listed above. Twenty three percent of respondents reported that there were no barriers to them accessing physiotherapy (Supplementary table 1).

Those who had access to physiotherapy rated their quality of life, as measured by the EQ-5D-3L index, to be significantly better compared to those who did not have access ($p=0.048$) (Table 5). Those who were currently receiving physiotherapy for their multiple sclerosis had a significantly lower psychological impact of multiple sclerosis, as

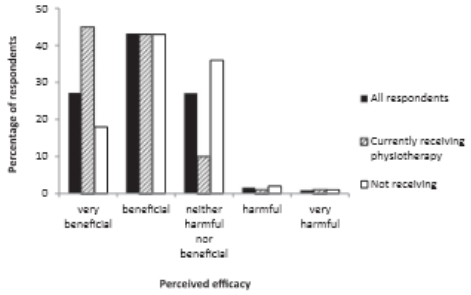

Fig. 1. Perceived efficacy of physiotherapy.

measured by the MSIS-29 psychological sub-scale, compared to those who were not receiving physiotherapy ($p=0.019$). However, those who had access and those who were currently receiving physiotherapy were younger and had a shorter time since diagnosis (all $p < 0.05$) than those who did not have access and were not receiving physiotherapy. There were no other statistically significant differences between the EQ-5D-3L index and MSIS-29 sub scale scores and physiotherapy provision (Table 5).

In total 38% (n=462) of respondents had used complementary and alternative therapies for their multiple sclerosis in the prior three months (Table 6). The three most commonly used complementary and alternative therapies were massage (17%), reflexology (12%) and relaxation or meditation (10%).

4. Discussion

This was the largest United Kingdom based survey of solely people with progressive multiple sclerosis and the first to explore access, delivery and efficacy of physiotherapy services in this patient group in the United Kingdom. Access to physiotherapy in this sample was high (87%), with approximately one third currently receiving physiotherapy for their multiple sclerosis. A recent survey of people with all types of multiple sclerosis in the United Kingdom found 17% of respondents did not have access (MS Society, 2016b). This is similar to the present results in which 13% of respondents did not have access to physiotherapy services. In addition the MS Society report suggested 32% of people with multiple sclerosis were receiving physiotherapy from non-National Health Service providers, compared to 42% in the present study. Although the results are similar, the slight discrepancies may be explained by differences in multiple sclerosis sub-type. The present study focussed on people with progressive forms of multiple sclerosis who may have a greater need of physiotherapy.

Table 4.
Expected waiting times by source of physiotherapy.

Physiotherapy provider		Expected waiting time (weeks)					
		< 1	1–2	2-4	4-6	6–12	> 12
NHS	n=133	2%	22%	15%	26%	23%	10%
Non-NHS	n= 26	27%	39%	23%	0%	12%	0%
Both	n=27	7%	11%	33%	11%	19%	19%

NHS: National Health Service; n: number of responses.

Table 5
Associations between access to and receiving physiotherapy and respondent demographics.

Variable		Access to physiotherapy			Receiving physiotherapy		
		n	median	p	n	median	p
EQ-5D-3L index	Yes	1099	0.57	0.048[a]	401	0.57	0.778
	No	167	0.50		852	0.57	
MSIS-29 phys	Yes	1113	56	0.199	411	57	0.83
	No	173	58		871	57	
MSIS-29 psych	Yes	1102	19	0.435	403	19	0.019[a]
	No	170	20		865	20	
Time since diagnosis	Yes	1082	14.5	0.034[a]	680	14.0	0.009[a]
	No	165	17.0		158	17.0	
Age	Yes	1118	59	< 0.001[a]	704	59	< 0.001[a]
	No	173	61		166	61	
Urban dwelling	Yes	746	–	0.418	273	–	0.913
	No	110	–		581	–	
Rural dwelling	Yes	330	–		125	–	
	No	57	–		260	–	

n: number of responses; EQ-5D-3L: EQ-5D-3L Health Questionnaire; MSIS-29 – phys: Multiple Sclerosis Impact Scale physical sub-scale; MSIS-29 – psych: Multiple Sclerosis Impact Scale psychological sub-scale; PPMS: Primary Progressive Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis.
[a] Statistically significant from Mann-Whitney test.

The most common setting of physiotherapy delivery was in a hospital or clinical environment (46%). This is in line with another report from the MS Society which, whilst calling for more community based care, found that the majority of multiple sclerosis care is delivered in the hospital setting (MS Society, 2016a).

In the United Kingdom, target waiting times for therapies, not

Table 3
Perceived efficacy of physiotherapy interventions received by respondents.

Intervention	% of total n	very harmful	harmful	neither harmful nor beneficial	beneficial	very beneficial
Home exercise programme	86	0	1	12	58	28
Exercise with physiotherapist	74	< 1	< 1	6	39	54
Advice/Education	67	0	< 1	8	50	41
FES	25	0	3	21	29	47
Standing frame	18	0	3	8	53	37
Acupuncture	10	2	5	36	31	26
TENS	7	3	10	34	34	17
Other[a]	5	–	–	–	–	–

Total respondents n=452. All values are percentages. Participants were able to choose more than one option.
n: number of respondents; FES: functional electrical stimulation; TENS: transcutaneous electrical nerve stimulation.
[a] interventions named as 'other' all had n < 10 and included: hand physiotherapy, women's health physiotherapy, medication, orthotics, manual therapies, whole body vibration, and walking aid prescription.

Table 6.
Complementary and alternative therapies used in the prior three months.

Complementary and alternative medicine	n	%
Massage	207	17
Reflexology	146	12
Relaxation or meditation	123	10
Hyperbaric oxygen therapy	85	7
Acupuncture or acupressure	72	6
Osteopathy or chiropractic	58	5
Homeopathy or herbal medicine	40	3
Reiki	33	3
Aromatherapy	32	3
Magnet field therapy	9	< 1
The Alexander technique	7	< 1
Other	29	2
None	747	62

Total responders n=1209, participants were able to choose more than one option.
Complementary and alternative medicines named as 'other' (all n < 7): action potential stimulation; bee venom; Bowen technique; 'circulation booster'; craniosacral therapy; diet management; low dose Naltrexone; 'muscle activation therapy'; SCENAR device; and supplements.

specifically physiotherapy, range from 14 to 21 weeks (JJ Consulting, 2011). Overall 90% of this sample reported an expected waiting time for a physiotherapy appointment of 12 weeks or less. However, expected waiting times varied depending on service provider: 89% of those receiving their physiotherapy only from non-National Health Service providers reported an expected waiting time of just four weeks or less compared to 39% of those receiving their physiotherapy from the National Health Service. The overall result (90% waiting 12 weeks or less to see a physiotherapist) is different from a United Kingdom wide report by the Chartered Society of Physiotherapy which reported that 83% of neurology outpatients were seen by a Neurology physiotherapist in eight weeks or less (JJ Consulting, 2011). Differences may be due to this sample being made up solely of people with progressive multiple sclerosis and the question asked was in regard to expected waiting times.

Respondents were generally positive in their opinion of physiotherapy with 70% of respondents reporting it to be either 'beneficial' or 'very beneficial' to them. Indeed only 3% thought that physiotherapy had a negative effect. The most commonly received interventions were also perceived to be the most beneficial. All of the physiotherapy interventions which participants received, apart from acupuncture, have evidence to support their effectiveness in people with progressive multiple sclerosis (Campbell et al., 2015).

The three most common interventions received, home exercise programme, exercise with a physiotherapist and advice, were also reported as being the most beneficial. Our previous systematic review found strong evidence to support the use of exercise to improve mobility and function in multiple sclerosis (Campbell et al., 2015). In addition patient education has been found to increase disease knowledge in patients with multiple sclerosis (Kopke et al., 2014). One intervention, transcutaneous electrical nerve stimulation, was generally reported to be beneficial although 13% reported it to be potentially harmful. This negative opinion is in contrast with two systematic reviews which concluded that transcutaneous electrical nerve stimulation was both safe and effective for treating spasticity (Fernandez-Tenorio et al., 2016) and pain (Sawant et al., 2015) in multiple sclerosis although the type of multiple sclerosis may have an impact upon efficacy (Sawant et al., 2015).

The most commonly reported and greatest barriers to accessing physiotherapy can be categorised as logistical (transport issues, needing someone to go with them) and symptomatic (mobility, fatigue, continence and pain). A study by Asano et al. found similar barriers to participating in exercise in people with multiple sclerosis (Asano et al., 2013). An increase in care close to home could address the logistical barriers and potentially reduce the impact of the symptomatic barriers. Indeed the recent report from the UK MS Society called for more community based care (MS Society, 2016a). Simple solutions such as the timing of appointments to address fatigue and ensuring adequate and clearly signposted toilet facilities to address concerns with continence may also be considered.

Having access to physiotherapy was associated with better quality of life and currently receiving physiotherapy was associated with less of a psychological impact of multiple sclerosis but not physical impact. As this was a cross-sectional study it was not possible to draw causality between these variables. Having access to, or receiving, physiotherapy was not associated with urban or rural dwelling. This is in contrast to research conducted in the Republic of Ireland which found a lack of access to physiotherapy in people with multiple sclerosis from rural areas (MacLurg et al., 2005). A greater proportion of Ireland's population does however live rurally (37% compared to 18% in the United Kingdom) which may account for the differences in results (World Data Bank, 2016).

Thirty eight percent of this sample had used a complementary and alternative therapy in the past three months for their multiple sclerosis. This result was lower than complementary and alternative therapies use in Germany (67%) (Apel et al., 2006), the United States of America (58%) (Stoll et al., 2012) and the Nordic countries (46–58%) (Skovgaard et al., 2012) but higher than complementary and alternative therapies use in Turkey (26%) (Gedizlioglu et al., 2015). The majority of the participants in the studies which reported higher complementary and alternative therapies usage had relapsing remitting multiple sclerosis and were mildly or moderately affected. In addition, a study in Germany found that the majority of complementary and alternative therapies use by people with multiple sclerosis happens in the early stages of the disease as initially they explore all avenues (Kochs et al., 2014). As the participants in this sample had a mean time since diagnosis of 16 years this may explain why complementary and alternative therapies use was lower that most of previous research where, when reported, time since diagnosis was from seven to nine years (Apel et al., 2006; Gedizlioglu et al., 2015).

5. Limitations

This study had a number of limitations. The cross-sectional design does not allow for causality to be drawn between associations. There was the potential for sample bias as those who engage with the UK MS Register may be more likely to seek out and engage with services. Furthermore, the diagnosis of multiple sclerosis type was self-reported, however in future the UK MS Register intends to be linked with clinical data from the National Health Service. A lack of geographical data from those in Northern Ireland meant that comparison of rural and urban dwelling in this part of the country was not possible limiting the nationwide applicability of the result. Due to the programming of the survey some participants were able to complete it without answering all of the questions and due to the low number of participants who completed the question regarding expected time to wait for an appointment this meant only 192 participants answered every single question. Subsequently percentages were calculated from the number of respondents to each question. Finally, the number of people who had access to physiotherapy was 6.5 times greater than the number of people who did not, as such results comparing these two groups should be interpreted with some caution.

6. Conclusion

This was the first study to focus on physiotherapy access and use by people with progressive multiple sclerosis in the United Kingdom and as such provides a unique insight. Overall this study has shown that access and perceived efficacy of physiotherapy is high in the United Kingdom amongst people with progressive multiple sclerosis. However, 13% did not have access to physiotherapy which indicates a gap in

Appendix 3 – Access to and use of clinical services and disease-modifying therapies by people with progressive multiple sclerosis in the United Kingdom

MS CARE DELIVERY: CHALLENGES AND INNOVATIONS

Access to and Use of Clinical Services and Disease-Modifying Therapies by People with Progressive Multiple Sclerosis in the United Kingdom

Evan Campbell, MRes; Elaine H. Coulter, PhD; Paul Mattison, MD; Angus McFadyen, PhD; Linda Miller, MPhil; Lorna Paul, PhD

Background: *According to current UK guidelines, everyone with progressive multiple sclerosis (MS) should have access to an MS specialist, but levels of access and use of clinical services is unknown. We sought to investigate access to MS specialists and use of clinical services and disease-modifying therapies (DMTs) by people with progressive MS in the United Kingdom.*

Methods: *A UK-wide online survey was conducted via the UK MS Register. The inclusion criteria were age 18 years or older, primary or secondary progressive MS, and a member of the UK MS Register. Participants were asked about access to MS specialists, recent clinical service use, receipt of regular review, and current and previous DMT use. Participant demographic data, quality of life, and disease impact measures were from the UK MS Register.*

Results: *In total, 1298 individuals responded: 7% were currently taking a DMT, 23% had previously taken a DMT, and 95% reported access to an MS specialist. The most used practitioners were MS doctors/nurses (50%), general practitioners (45%), and physiotherapists (40%). Seventy-four percent of participants received a regular review, although 37% received theirs less often than annually. Current DMT use was associated with better quality of life, but past DMT use was associated with poorer quality of life and higher impact of disease.*

Conclusions: *Access to and use of MS specialists was high. However, a gap in service provision was highlighted in both receipt and frequency of regular reviews.* ***Int J MS Care.*** **2017;19:275–282.**

Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease of the central nervous system that results in axonal and gray matter loss. It is estimated that there are 130,000 people living with MS in the United Kingdom.[1] At the time of diagnosis, approximately 15% of people with MS are diagnosed as having primary progressive MS (PPMS); 80%, relapsing-remitting MS (RRMS); and 5%, progressive relapsing MS.[2] Approximately 80% of those with RRMS will go on to develop secondary progressive MS (SPMS).[2]

Disease-modifying therapies (DMTs) are currently available to those who have RRMS or who are still experiencing relapses in the early stages of SPMS. Disease-modifying therapies have been found to delay the transition from RRMS to SPMS.[3] Until recently, there

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DOI: 10.7224/1537-2073.2017-022

were no effective licensed pharmacologic treatments for slowing the progression of disability in either PPMS or SPMS; however, ocrelizumab has now been shown to decrease disability progression by 25% in people with PPMS.[3] Due to the lack of available effective pharmacologic treatments for disease activity in progressive MS, specialist rehabilitation services are of particular importance. Despite this, access to specialist services throughout the United Kingdom can be difficult, and people with progressive MS are often told that there is little available for them and are advised to self-manage their condition.[4] The International Progressive MS Alliance has subsequently highlighted rehabilitation for people with progressive MS as a research priority,[5] and disciplines such as physiotherapy have positive evidence in the rehabilitation of people with progressive MS.[6]

The current National Institute for Health and Care Excellence guidelines for MS and Healthcare Improvement Scotland Clinical Standards for Neurological Health Services state that everyone with MS in the United Kingdom should have access to an MS specialist and receive a comprehensive regular review at least annually by a member of a multidisciplinary MS team.[7,8] This review should cover all aspects of care (including medication, symptom management, disease course, general health, participation, and social care needs) and does not have to be conducted in a clinical environment. Recently, MS specialist nurses were found to be the most consulted health-care professionals,[9] and 86% of people with MS reportedly had access to a neurologist or an MS nurse.[10] However, these studies did not differentiate between MS types. In some areas of the United Kingdom, such as London and Northern Ireland, limited MS service provision has been found.[11,12] Furthermore, in England and Wales, 55% of patient comments regarding provision of National Health Service (NHS) MS services were negative.[13]

The purpose of this study was to investigate access to and use of clinical services for people with PPMS and SPMS, specifically, exploring whether people with progressive MS had access to an MS specialist, what clinical services they used, if they received a regular review, their current and previous use of DMTs, and associations between these variables and quality of life and the physical and psychological impact of MS.

Methods

UK MS Register

The UK MS Register is an online register funded by the MS Society. People with MS become members voluntarily, and they answer both regular and online surveys.[14] Members self-report their MS diagnosis type and demographic information and complete self-report outcome measures, such as the three-level version of the EQ-5D (EQ-5D-3L) health questionnaire (EuroQol) and the physical and psychological subscales of the 29-item Multiple Sclerosis Impact Scale (MSIS-29) every 3 months. Data are anonymized using the Secure Anonymised Information Linkage system.[15] At the time of this study there were 11,041 people on the UK MS Register, with 4384 people active on the Register in the previous 6 months.

Design and Participant Recruitment

A cross-sectional survey design was used. The survey was available on the UK MS Register from August to October 2015. To be eligible for inclusion, a participant had to be 18 years or older, living in the United Kingdom, diagnosed as having progressive MS, and registered on the UK MS Register. Potential participants were identified by the UK MS Register and were informed of the survey by e-mail. The survey was accessed only via the UK MS Register, and completion was regarded as informed consent. Ethics approval was obtained from the College of Medical, Veterinary, and Life Sciences Ethics Committee, University of Glasgow, and the study underwent peer review by the information governance panel of the UK MS Register (South West–Central Bristol Research Ethics Committee [Ref: 11/SW/0160]).

The survey was in two sections. The first asked about access to, experiences with, and opinions of physiotherapy services and complementary therapies in the United Kingdom and has been described elsewhere.[16] The second section asked whether a participant had access to an MS specialist, defined as a clinician with MS specialist skills. Participants were also asked which clinicians they consulted in the previous 3 months for their MS. Participants were asked whether they received a regular review for their MS, how often that review took place, who normally undertook the review, and where the review normally took place. Finally, previous and current use of DMTs was explored, and participants were asked to select whether they were currently taking, or had previously taken, any of the following: beta-interferon (Rebif [EMD Serono Inc, Rockland, MA], Avonex [Biogen, Cambridge, MA], Betaseron [Bayer HealthCare Pharmaceuticals, Montville, NJ]), glatiramer acetate (Copaxone [Teva Pharmaceutical Industries Ltd, North Wales, PA]), dimethyl fumarate (Tecfidera [Biogen]), teriflu-

nomide (Aubagio [Genzyme Corp, Cambridge, MA]), natalizumab (Tysabri [Biogen], Antegren [Biogen]), fingolimod (Gilenya [Novartis Pharmaceuticals Corp, East Hanover, NJ]), mitoxantrone (Novantrone [EMD Serono Inc, Rockland, MA]), and alemtuzumab (Lemtrada [Genzyme Corp]). A copy of the survey is available on request. Due to the structural progression of the survey, not all participants answered all questions.

Access

This study explored two components of access: the opportunity to enter into the service (regardless of organizational barriers such as waiting times and distance to travel) and the use of services.[17] In this survey, these two components were referred to as *access* and *use*, respectively. Although these terms were not explicitly explained, their meaning was implied by questions asked; for example, "Which of the following clinicians could you see if you wanted to?" implied the availability of the opportunity to see a clinician and "Which of the following clinicians have you seen in the past 3 months for your MS?" implied the use of services. Barriers to accessing physiotherapy were explored in some detail and have been published elsewhere.[16]

Access to an MS Specialist

Participants were asked whether they had access to an MS specialist service. If they answered "yes" they were then asked which clinicians they had seen recently for their MS. If they answered "no" they were then asked which clinicians they could see if they wanted to. Included in this list were MS specialist nurse and MS specialist doctor/neurologist. The answers of those who reported having access to an MS specialist service and of those who reported that they could see an MS specialist nurse or doctor were combined. This gave the total level of access to MS specialists for this cohort.

Additional Data from UK MS Register

In addition to data collected from the survey, the following data routinely collected by the UK MS Register were accessed: type of MS, age, sex, time since diagnosis of MS, quality of life as measured by the EQ-5D-3L, the physical and psychological subscale scores of the MSIS-29, and Lower Super Output Area codes (England and Wales) and Output Area codes (Scotland) (there were no available geographic data for participants from Northern Ireland). Lower Super Output Area codes and Output Area codes, which are used to tabulate census and statistical data by the Office of National Statistics, were combined with data available from the Office for National Statistics and the Scottish Office for National Statistics[18,19] to generate the following information: rural or urban dwelling and Strategic Health Authority for participants in England (in 2013, NHS England divided England into ten regions called Strategic Health Authorities, each of which contained multiple NHS trusts). Rural dwelling was defined as a settlement with a population of 10,000 or less.[20]

The EQ-5D-3L is a self-report measure of quality of life generating an index ranging from −1 to 1, with a higher index indicating a better quality of life.[21] The MSIS-29 is a 29-item self-report measure with physical and psychological subscales to measure the impact of MS.[22] The physical subscale score ranges from 20 to 80, and the psychological subscale score ranges from 9 to 36. A lower score indicates a lower impact of MS.

Data Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY). Descriptive statistics were used to characterize demographic data and all the outcome variables. Due to programming and structure of the survey not all participants answered every question, therefore, responses to individual questions are presented as percentages of number of respondents to that question. Data were tested for normality, and due to nonnormal distribution, χ^2 and Mann-Whitney tests were used as appropriate. A significance level of $P < .05$ was used.

Results

Of 2538 registrants with progressive MS who were e-mailed by the UK MS Register, 1298 completed the survey, generating a 51% response rate (England: n = 1030, Scotland: n = 130, Wales: n = 104, and Northern Ireland: n = 21 [13 participants had not supplied their geographic data to the UK MS Register]). Participants had a mean (SD) age of 59 (8) years and time since diagnosis of 16 (9) years; the female-male ratio was 1.7:1; 486 (37%) had PPMS and 812 (63%) had SPMS. The mean (SD) EQ-5D-3L index was 0.49 (0.20), indicating a poorer quality of life compared with the general population of the same age who would have an approximate index of 0.8.[23] The mean (SD) MSIS-29 physical and psychological subscores were 55.97 (12.64) and 19.96 (6.10), respectively, indicating that this sample was moderately affected physically and psychologically by

their MS (Table 1). Compared with those with SPMS, people with PPMS were older and had a shorter time since diagnosis, a higher EQ-5D-3L index, and lower psychological and physical scores on the MSIS-29 (all $P < .005$).

In total, 1184 participants (95%) reported that they had access to an MS specialist, and 959 (81%) of those who had access reported they would be able to access the specialist if their symptoms or needs changed. Figure 1 shows access to MS specialists across the United Kingdom. Access to an MS specialist ranged from 92% in Yorkshire and the Humber and the East Midlands to 98% in Wales.

Overall, 1046 participants (81%) reported using clinical services for their MS in the previous 3 months. The most commonly used clinical services were MS specialist doctors/nurses (n = 517 [49%]), general practitioners (n = 467 [45%]), and physiotherapists (n = 414 [40%]) (Figure 2). Of the participants receiving clinical services for their MS, 481 (46%) were receiving a single service and 565 (54%) were receiving more than one service. Of the 447 participants who answered the question, 88 (20%) reported that they were currently taking a DMT (PPMS: n = 18, SPMS: n = 70). Of the 1241 participants who answered the question, 303 (24%) reported that they had previously taken a DMT (PPMS: n = 37, SPMS: n = 266). This equated to 7% of the sample currently taking a DMT and 23% having previously taken a DMT.

In total, 917 of 1243 participants (74%) received a regular review; 505 (55%) received that review annually. Of 911 respondents, 569 (63%) had their review performed by an MS specialist doctor, and 248 (27%) reported that it was performed by a nurse. A total of 819 of 911 participants (90%) reported usually receiving their review in a hospital or clinic (Table 2). Ninety per-

Table 1. Demographic characteristics of survey participants

Characteristic	Total (N = 1298)	PPMS (n = 486)	SPMS (n = 812)	*P* value, difference between PPMS and SPMS
Age, mean (SD), y	59 (8)	60 (8)	58 (9)	<.001[a]
Time since diagnosis, mean (SD), y	16 (9)	12 (8)	19 (9)	<.001[a]
Sex, No.				<.001[b]
Female	824	246	578	
Male	474	240	234	
Country (where known), No.				.343
Scotland	130	57	73	
England	1030	372	658	
Wales	104	40	64	
Northern Ireland	21	9	12	
EQ-5D-3L index, mean (SD)	0.49 (0.20)	0.52 (0.20)	0.48 (0.20)	.001[a]
MSIS-29 psych score, mean (SD)	19.96 (6.10)	19.35 (6.05)	20.31 (6.11)	.004[a]
MSIS-29 phys score, mean (SD)	55.97 (12.64)	54.46 (13.27)	56.88 (12.12)	.002[a]

Abbreviations: EQ-5D-3L, three-level version of EQ-5D health questionnaire; MSIS-29, 29-item Multiple Sclerosis Impact Scale; phys, physical subscale; PPMS, primary progressive multiple sclerosis; psych, psychological subscale; SPMS, secondary progressive multiple sclerosis.
Note: Not every participant had demographic data available (eg, country of domicile). Mean (SD) time between survey completion and most recent EQ-5D-3L and MSIS-29 completions were 39 (120) and 19 (111) days, respectively.
[a]Statistically significant as calculated by Mann-Whitney tests.
[b]Statistically significant as calculated by χ^2 tests.

Table 2. Survey responses regarding a regular review for progressive MS

Question and answer	Responses, No. (%)
Are you offered a regular clinical review for your MS? (n = 1243)	
Yes	917 (74)
No	287 (23)
Don't know	39 (3)
On average, how often is your review? (n = 912)	
Twice a year	57 (6)
Once a year	505 (55)
Less frequently than once a year	341 (37)
Don't know	9 (1)
Who usually undertakes your review? (n = 911)	
MS specialist doctor/neurologist	569 (63)
GP	8 (1)
Nurse	248 (27)
Physiotherapist	12 (1)
Occupational therapist	6 (1)
The person can vary	58 (6)
Other	10 (1)
Where does your review normally take place? (n = 911)	
At home	43 (5)
In a hospital or clinic	819 (90)
In a community center	10 (1)
GP surgery	20 (2)
Other	19 (2)

Abbreviations: GP, general practitioner; MS, multiple sclerosis.

cent of participants who were currently taking a DMT received a regular review: 6% received their review twice a year, 51% once a year, 41% less frequently than once a year, and 2% did not know (data not shown).

There was a significant association between access to an MS specialist and receiving a regular review ($P < .001$) (Table 3). Access to an MS specialist was not associated with MS type, past or present DMT use, or urban/rural dwelling (Table 3).

Participants who received a single clinical service, as opposed to multiple services, for their MS had a better quality of life as measured by the EQ-5D-3L index ($P < .001$) and less of a physical and psychological impact of MS as measured by the MSIS-29 ($P < .001$). Use of single or multiple services was, however, not dependent on MS type (n=1045, $P = .165$) or whether a participant lived in a rural or urban location (n = 1003, $P = .972$) (data not shown). Participants who were currently taking a DMT for their MS had a better quality of life ($P = .016$) than those who were not taking a DMT. Those who had previously taken DMTs, however, had a poorer quality of life ($P < .001$) and greater physical ($P < .001$) and psychological ($P = .006$) impacts than those who had not taken DMTs (Table 4). There were no differences in quality of life and disease impact scores between those who did and did not have access to an MS specialist or access to a review, and there was no difference in the psychological or physical impact of MS between those who were and were not currently taking a DMT (Table 4).

Table 3. Associations between access to an MS specialist and MS type, DMT use, dwelling location, and receipt of regular review

	Participants, No.	*P* value
Access to an MS specialist and:		
PPMS or SPMS	1248	.473
Past DMT use	1227[a]	.371
Current DMT use	362[a]	.175
Urban/rural dwelling	1201	>.99
Receipt of regular review	1233	<.001[b]

Abbreviations: DMT, disease-modifying therapy; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
[a]Numbers are significantly higher than results of current and past DMT use reported in main text (88 and 303, respectively) because χ^2 test also includes the participants who answered "no."
[b]Statistically significant result from χ^2 test.

Table 4. Differences in EQ-5D-3L and MSIS-29 scores by access to an MS specialist, regular review, receipt of MS service, and DMT use

	Participants, No.	Score, median	Participants, No.	Score, median	*P* value
Access to MS specialist	Yes		No		
EQ-5D-3L	1154	0.57	62	0.50	.245
MSIS-29 phys	1180	56.00	64	58.50	.581
MSIS-29 psych	1167	19.00	63	19.00	.832
Access to review	Yes		No		
EQ-5D-3L	898	0.57	276	0.57	.642
MSIS-29 phys	914	56.00	286	58.00	.187
MSIS-29 psych	903	19.00	285	19.00	.410
Single/multiple services	Single		Multiple		
EQ-5D-3L	469	0.57	548	0.50	<.001[a]
MSIS-29 phys	478	55.00	563	59.00	<.001[a]
MSIS-29 psych	473	18.00	555	20.00	<.001[a]
Current DMT use	Yes		No		
EQ-5D-3L	87	0.57	346	0.50	.016[a]
MSIS-29 phys	87	56.00	359	60.00	.050
MSIS-29 psych	85	20.00	357	20.00	.960
Past DMT use	Yes		No		
EQ-5D-3L	296	0.50	912	0.57	<.001[a]
MSIS-29 phys	302	59.00	935	56.00	<.001[a]
MSIS-29 psych	299	20.00	925	19.00	.006[a]

Abbreviations: DMT, disease-modifying therapy; EQ-5D-3L, three-level version of EQ-5D-3L health questionnaire; MS, multiple sclerosis; MSIS-29, 29-item Multiple Sclerosis Impact Scale; phys, physical subscale; psych, psychological subscale.
Note: Not all participants had EQ-5D-3L or MSIS-29 data available, accounting for the slight variations in numbers.
[a]Statistically significant as calculated by Mann-Whitney tests.

Discussion

To our knowledge, this study had the largest sample solely of people with progressive MS to be surveyed to date and was the first to investigate access to and use of clinical services for people with progressive forms of MS across the United Kingdom.

In this sample of 1298 individuals with MS, access to an MS specialist was high (95%) and was similar across the United Kingdom (Figure 1). This was slightly higher than the outcome of a survey performed by the MS Society in people with all types of MS in the United Kingdom that reported that 86% of participants had access to a neurologist or MS nurse.[10] A previous study conducted in London reported a lack of access to MS-related services among those severely affected by MS[11]; however, the present study indicates that 95% of people with progressive MS have access to an MS specialist. This difference in results may indicate improvements in service provision since Edmonds et al.[11] performed their study and that the people in this sample were not severely affected by their MS. Interestingly, there were no differences in quality of life and disease impact measures between those who did and those who did not have access to an MS specialist. However, there were relatively few people who did not have access in these analyses, so results should be interpreted with caution.

***Figure 1.* Access to multiple sclerosis (MS) specialists across United Kingdom**

Access to MS specialists by people with progressive MS in Scotland, Northern Ireland, Wales, and Strategic Health Authorities in England.

Although access to MS specialists was high, not all received a regular review, as is recommended by current guidelines and standards.[7,8] Just less than three-quarters of participants received a regular review, and 37% of these received their review less frequently than annually. This is a breach of the National Institute for Health and Care Excellence guidelines and the Healthcare Improvement Scotland clinical standards. With the potential advent of pharmacologic treatments for PPMS disease activity,[3] a regular clinical review will in the future be particularly important in the care of people with progressive MS. Indeed, of those who were currently receiving a DMT, 90% were in receipt of a regular review, but only 57% received that review once a year or more frequently. However, note that there were no differences in quality of life or disease impact measures between those who did and did not receive a regular review.

Use of clinical services in this study's participants was high. The three most used clinical services were MS specialist nurses or doctors, general practitioners, and physiotherapists (Figure 2). This finding was similar to two previous studies surveying people with all types of MS in the United Kingdom and Europe.[9,24] This may indicate that people with progressive MS are using the same kinds of clinical services as those with RRMS.

Similar proportions of participants received multiple services (54%) or a single service (46%) for their MS. Those who received a single service for their MS had a better quality of life and lower psychological and physical impacts of MS compared with those who received

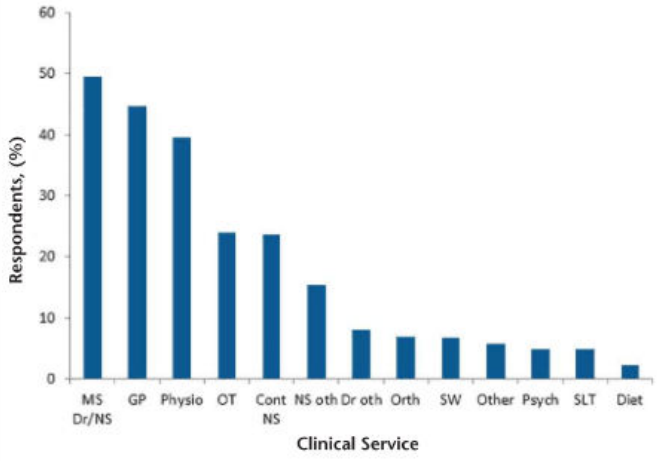


***Figure 2.* Clinical services used by participants for their multiple sclerosis (MS) in past 3 months**

Abbreviations: Cont NS, continence nurse; Diet, dietitian; Dr oth, doctor other; GP, general practitioner; MS Dr/NS, MS doctor or MS nurse; NS oth, nurse other; Orth, orthotist; OT, occupational therapist; Physio, physiotherapist; Psych, psychologist; SLT, speech and language therapist; SW, social worker.

multiple services, which may be a reflection of clinical need and, in turn, is likely to be associated with disability level.

There was no association between rural or urban dwelling and access to an MS specialist or receiving a regular review. Previous research by Lonergan et al.[25] in the Republic of Ireland found that a lack of access to services was associated with rural dwelling. These researchers, however, surveyed people with all types of MS, and 37% of the population live rurally in the Republic of Ireland, compared with 18% in the United Kingdom,[26] which may explain the differences in results reported. Furthermore, the lack of association between rural and urban living and access to an MS specialist may be due to the definition of access used in this study being the opportunity to see a clinician regardless of personal and organizational barriers.

Seven percent of this sample was currently taking a DMT, and 23% had been prescribed them previously. This result is lower than previously reported by the MS Society, which found that 56% of all people with all types of MS in United Kingdom were taking a DMT.[10] This difference is expected as prescribing guidelines state that DMTs are not effective in progressive forms of MS when relapses are not present[27] and that those taking a DMT currently may have been prescribed them while in the relapsing-remitting phase of MS. The 7% of participants still taking a DMT does, however, contribute further to the importance of a regular clinical review because there are potentially a large number of people with MS inappropriately taking these drugs in the United Kingdom. Furthermore, those taking a DMT had a better quality of life compared with those who were not. Those who had previously taken DMTs, however, had a poorer quality of life and greater physical and psychological impacts of MS compared with those who had never taken them. These differences were, however, small and may be an indication of the stage of disease because those who are no longer taking a DMT may have more advanced disease and may have transitioned into the secondary progressive phase, for which DMTs are no longer appropriate.

This study has several limitations. The open and voluntary nature of the UK MS Register and online surveys leaves the sample open to bias to the motivated and those with a vested interest. In addition, those who are more severely disabled and find it difficult to access services may not be on the register. The diagnosis and type of MS was self-reported, but in the future the UK MS

PracticePoints

- The level of access to MS specialists by people with progressive MS in the United Kingdom was 95%.
- The most used practitioners by participants for their MS were MS specialist doctors/nurses, general practitioners, and physiotherapists.
- The level of access to a regular clinical review was 74%; however, 37% of participants received their reviews less often than annually, falling short of the recommended guidelines.

Appendix 4 – Full online survey

Below is a copy of the online survey used to collect data for chapters 4 – 6. It comprises an introduction and then three sections of questions. The text in italics next to questions is the instructions for logical progression that were given to the UK MS Register.

Introduction

You have been invited to take part in this study by answering a questionnaire regarding your experiences of physiotherapy. You have been selected because you have a progressive form of MS and are registered on the UK MS Register. It is up to you to decide whether or not to take part. There are no risks involved in taking part and you will remain anonymous. If you decide to start the questionnaire you are free to stop at any point. Filling in the questionnaire completely or in part indicates consent to take part in this study. If you have problems using a computer it is appropriate for someone to fill in the answers for you as long as the answers are your own.

The purpose of this questionnaire is to find out if you receive physiotherapy as a treatment for your MS, if physiotherapy is available to you, what you think of physiotherapy, how you would like your physiotherapy delivered and what other therapies you receive for your MS.

Physiotherapy can mean different things to different people. There are many different treatments that are classed as physiotherapy. In this questionnaire, physiotherapy means any treatment that is carried out by a physiotherapist or a physiotherapy assistant.

Section 1. This section is about the physiotherapy you receive and what you think of it.

Q1.1 Do you receive physiotherapy at the moment? (Please tick the most appropriate box)

- Yes *if yes go to Q 1.3.a*
- No *if No go to Q 1.2*

Q1.2 Could you get physiotherapy if you wanted it? (Please tick the most appropriate box)

- Yes *if yes go to Q1.3.b*
- No *if no go to Q1.5b*

Q1.3.a Who refers you to the physiotherapist? (Please tick all that apply)

- MS specialist Doctor/Neurologist
- GP
- I self-refer
- MS specialist nurse
- Other (please state) _____
- Don't know *go to question 1.4*

Q1.3.b If you wanted to see a physiotherapist, what would you do? (Please tick all that apply)

- Ask the MS specialist Doctor/Neurologist
- Ask your GP
- Self-refer
- Ask MS specialist nurse
- Other (please state) _____
- Don't know *go to question 1.4*

Q1.4 To the best of your knowledge what type of organisation provides your physiotherapy at the moment? (Please tick all that apply)

- NHS (National Health Service)

- Private (self-funded)
- Private (insurance company, or equivalent, funded)
- Charity
- Other (please state) _____ *if answered yes to Q1.1 go to Q 1.5.a. all other options go to Q1.5.b*

Q1.5a Please describe the effect you think physiotherapy has on you at the moment. (Please tick the most appropriate box)
Likert scale:
very beneficial, beneficial, neither harmful nor beneficial, harmful, very harmful
go to Q1.6

Q1.5b Please describe the effect you think physiotherapy would have on you at the moment? (Please tick the most appropriate box)
Likert scale:
very beneficial, beneficial, neither harmful nor beneficial, harmful, very harmful
if "very harmful", "harmful" or "neither harmful nor beneficial" chosen go to Q 3.1, all other answers go to Section Q2.1.

Q1.6 Please think about the physiotherapy that you received in the past 3 months. There are different types of physiotherapy treatment. From the list tick all that you have had in the past 3 months.

- Exercises to do on my own that were given to me by a physiotherapist
- Exercises with a physiotherapist
- FES (functional electrical stimulation)
- TENS (transcutaneous electrical stimulation)
- Standing frame or tilt table
- Acupuncture
- Advice or education from a physiotherapist
- other (Please state) _____ *all options go to Q1.7*

Q1.7 Now please describe the effect you think the different types of physiotherapy that you have received in the past 3 months have had on you. (Please tick the most appropriate box)

A list of interventions will be generated from the ticked boxes in question 6. Rate each with Likert scale.

very beneficial beneficial neither harmful nor beneficial harmful very harmful

all options go to Q1.8

Q1.8 Do you receive physiotherapy sessions regularly or does the frequency of your physiotherapy sessions depend on your symptoms? (Please tick the most appropriate box)

- I receive physiotherapy sessions regularly *go to Q 1.10*
- How often I receive physiotherapy varies depending on my symptoms *go to Q 1.9*

Q1.9 How long would **you expect** to wait for your physiotherapy appointment after asking/ being referred? (Please tick the most appropriate box)

- Less than a week
- 1 to 2 weeks
- 2 or more weeks but less than 4 weeks
- 4 or more weeks but less than 6 weeks
- 6 or more weeks but less than 12 weeks
- 12 or more weeks *all options go to Q1.11*

Q1.10 How **often** do you receive physiotherapy at the moment? This means that you had contact with the physiotherapist and received one of the treatments that you listed earlier. (Please tick the most appropriate box)

- once or more a week
- once a fortnight
- once every 1 to 3 months
- twice a year
- once a year or less *all options go to Q1.11*

Q1.11 How long do your physiotherapy sessions **usually** last? (Please tick the most appropriate box)

- up to half an hour
- between half an hour and an hour
- more than an hour *all options go to Q1.12*

Q1.12 There are different ways of receiving physiotherapy. Which of the following best describes the contact you have with your physiotherapist: (Please tick all that apply)

- Just the therapist and me
- In a small group of 2-4 people
- In a larger group of 5 or more people
- I receive my physiotherapy by the telephone or internet *all options go to Q1.13*

Q1.13 Where do you usually receive physiotherapy? (Please tick all that apply)

- At home
- In a hospital or clinic
- In a community centre
- In a charity centre
- Other (please state) _____ *all options go to Q2.1*

Section 2. This section is about how you would like to receive physiotherapy and factors that may restrict your ability to receive physiotherapy?

Q2.1 Do you **think you need** more physiotherapy than you receive at the moment? (Please tick the most appropriate box)

- Yes
- No
- Don't know *all options go to Q2.2*

Q2.2 Given the choice; would you prefer to receive physiotherapy regularly or for it to vary as you need it depending on your symptoms?

- Regularly *if regularly go to Q2.3*
- To vary depending on my symptoms *if to vary go to Q2.4*

Q2.3 Given the choice; how often would **you like** to receive physiotherapy? (Please tick the most appropriate box)

- once or more a week
- once a fortnight
- once every 1 to 3 months
- twice a year
- once a year or less *all options go to Q2.4*

Q2.4 Given the choice; how long would **you like** your physiotherapy sessions to last? (Please tick the most appropriate box)

- up to half an hour
- between half an hour and an hour
- more than an hour *all options go to Q2.5*

Q2.5 Given the choice; where would **you like** to receive physiotherapy? (Please tick the most appropriate box)

- At home
- In a hospital or clinic
- In a community centre
- In a charity centre
- Other (please state) _____ *all options go to Q2.6*

Q2.6 Given the choice; which of the following best describes how **you would like** your usual contact with your physiotherapist to be? (Please tick the most appropriate box)

- Just the therapist and me
- In a small group of 2-4 people
- In a larger group of 5 or more people
- I would like to receive my physiotherapy by the telephone or internet

all options go to Q2.7

Q2.7 Sometimes it is difficult for people with MS to receive physiotherapy treatment. From the following list tick all that restrict your ability to receive physiotherapy at the moment:

- pain
- fear of falling
- bladder or bowels problems
- fatigue
- depression
- anxiety/panic attacks
- difficulty with walking
- difficulty with wheelchair transfers
- transport problems
- distance to travel
- lack of suitable parking
- lack of time
- family commitments
- work commitments
- cost
- need someone to come with me
- personal issues with physiotherapist
- problems being referred to physiotherapy
- physiotherapy is not available
- physiotherapy will not be beneficial for me
- there is nothing that makes it difficult for me to receive physiotherapy
- other (please state) _____ *go to Q2.8 unless "there is nothing that makes it difficult for me to receive physiotherapy" is only one ticked in which case go to Q3.1*

Q2.8 From the list above order the 3 things, from 1 to 3, that restrict your ability for you to get physiotherapy the most (number 1 being the most restrictive).

List generated from Q2.7.

List vertically number 1 number 2 number 3

all options go to Q3.1

Section 3. This section is about other healthcare services that you receive for your MS.

Q3.1 Do you have access to an MS specialist service?

- Yes *go to Q3.2*
- No *go to Q3.3b*

Q3.2 Are you able to be referred or self-refer to this service if your symptoms or needs change?

- Yes
- No *all options got to Q3.3a*

Q3.3a What other health care professionals have you seen for your MS in the past 3 months? Please tick all that apply:

- Occupational therapist
- Social worker
- MS specialist nurse
- Continence nurse
- Nurse: other (please state) _____
- Psychologist
- GP
- MS specialist Doctor/Neurologist
- Doctor: other (please state) _____
- Speech and language therapist
- Dietician
- Orthotist
- Other _____ *all options go to Q3.4*

Q3.3b What other health care professionals would you be able to see for your MS if you wanted to? Please tick all that apply:

- Occupational therapist
- Social worker
- MS specialist nurse
- Continence nurse
- Nurse: other (please state) _____
- Psychologist

- GP
- MS specialist Doctor/Neurologist
- Doctor: other (please state) _____
- Speech and language therapist
- Dietician
- Orthotist
- Other _____ *all options go to Q3.3c*

Q3.3c From the list please tick all that you have seen in the past 3 months. List generated from Q3.3b with "I have not seen any of these in the past 3 months" as the last option. *All options go to Q3.4*

Q3.4 Are you offered a regular review for you MS? (This is an appointment to check to see how you are and if you have any unaddressed needs) (Please tick the most appropriate box for you)

- Yes *if yes go to Q3.5*
- No *if no go to Q3.8*
- Don't know *if don't know go to Q3.8*

Q3.5 On average; how often is your review? (Please tick the most appropriate box)

- Twice a year
- Once a year
- Less than once a year
- Don't know *all options go to Q3.6*

Q3.6 Who usually undertakes your review? (Please tick the most appropriate box)

- MS specialist Doctor/Neurologist
- GP
- Nurse
- Physiotherapist
- Occupational therapist
- The person who does my review can vary
- Other (please state) _____ *all options go to Q3.7*

Q3.7 Where does your review normally take place? (Please tick the most appropriate box)

- At home
- In a hospital or clinic
- In a community centre
- GP surgery
- Other (please state) _____ *all options go to Q3.8*

Q3.8 Which of the following medications have you ever taken? The original name of the drug is written first and then the brand name/names are written in brackets. (Please tick all that apply)

- Beta-interferon (Rebif, Avonex, Betaferon)
- Glatiramer acetate (Copaxone)
- Dimethyl fumarate (Tecfidera)
- Teriflunomide (Aubagio)
- Natalizumab (Tysabri, Antigren)
- Fingolimod (Gilenya, Novartis)
- Mitoxantrone (novantrone)
- Alemtuzumab (Lemtrada) *all options go to Q3.9 apart from "I have never"*
- I have never taken any of these medications *which goes to Q3.10*

Q 3.9 Which of the following medications do you currently take? The original name of the drug is written first and then the brand name/names are written in brackets. (Please tick all that apply)

- Beta-interferon (Rebif, Avonex, Betaferon)
- Glatiramer acetate (Copaxone)
- Dimethyl fumarate (Tecfidera)
- Teriflunomide (Aubagio)
- Natalizumab (Tysabri, Antigren)
- Fingolimod (Gilenya, Novartis)
- Mitoxantrone (novantrone)
- Alemtuzumab (Lemtrada)
- I do not currently take any of these medications *all options go to Q3.10*

Q 3.10 Complimentary therapies are forms of treatment that are not classed as medical but are often used in the treatment of MS. Which of the following complimentary therapies have you used/had for your MS in the past 3 months? (Please tick all that apply)

- Massage
- Reflexology
- Osteopathy or chiropractic
- Magnet field therapy
- The Alexander technique
- Acupuncture or acupressure
- Hyperbaric oxygen therapy
- Reiki
- Aromatherapy
- Relaxation or meditation
- Homeopathy or herbal medicine
- Other _____ *all options go to Q3.11*

Thank you very much for taking the time to complete this questionnaire.

Survey ends

Appendix 5 – Research questions that required more than one answer from the survey to be completed.

Research questions and the relevant questions from the survey

Research Question	Questions used from survey
What proportion of respondents have access to an MS Specialist?	3.1 Do you have access to an MS specialist service? 3.3b What other health care professionals would you be able to see for your MS if you wanted to?
What proportion of respondents use their MS Specialist?	3.3a What other health care professionals have you seen for your MS in the past 3 months? 3.3c What other health care professionals would you be able to see for your MS if you wanted to?
Which clinical services are used for their MS?	1.1 Do you receive physiotherapy at the moment? 3.3a What other health care professionals have you seen for your MS in the past 3 months? 3.3c What other health care professionals would you be able to see for your MS if you wanted to?
Multiple or single services used for MS?	1.1 Do you receive physiotherapy at the moment? 3.3a What other health care professionals have you seen for your MS in the past 3 months? 3.3c What other health care professionals would you be able to see for your MS if you

	wanted to?
What proportion of respondents have taken DMTs?	3.8 Which of the following medications have you ever taken? The original name of the drug is written first and then the brand name/names are written in brackets.
What proportion of respondents are currently taking DMTs?	3.9 Which of the following medications do you currently take? The original name of the drug is written first and then the brand name/names are written in brackets.
What proportion of respondents have access to physiotherapy?	1.1 Do you receive physiotherapy at the moment? 1.2 Could you get physiotherapy if you wanted it?
How do respondents get referred to physiotherapy?	1.3a Who refers you to the physiotherapist? 1.3b If you wanted to see a physiotherapist, what would you do?
What is the respondents' perceived efficacy of physiotherapy?	1.5a Please describe the effect you think physiotherapy has on you at the moment. 1.5b Please describe the effect you think physiotherapy would have on you at the moment?

Only the question is supplied, the possible answers to each question are not listed. These can be seen in full survey in Appendix 4

Appendix 6 – Ethics committee approval letter

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

Mr Evan Campbell
PhD student
The University of Glasgow
The University of Glasgow
59 Oakfield Avenue
Glasgow
G12 8LL

West of Scotland REC 4
Research Ethics
Clinical Research and Development
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SW
(Formerly Yorkhill Childrens Hospital)

Date 18 January 2017
Direct line 0141 232 1807
E-mail WoSREC4@ggc.scot.nhs.uk

Dear Mr Campbell

Study title: **The effect of High Intensity Interval Training on cardiovascular fitness in people with progressive Multiple Sclerosis.**
REC reference: **17/WS/0005**
Protocol number: **1**
IRAS project ID: **214650**

The Research Ethics Committee reviewed the above application at the meeting held on 06 January 2017. Thank you for attending to discuss the application with Dr Elaine Coulter.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request.
Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

1. Please confirm in writing (cover letter) that MOCA will not be used to assess capacity and update the supporting documents as deemed appropriate i.e. protocol.

2. Changes required to the PIS

   a. Please provide lay title similar to the one in the poster in addition to the full study title.
   b. On page 1, under the section "Why is this important?", line 1, please delete, "....early death and ...". This is to soften the paragraph.
   c. Please move the text in the section "What is interval training?" to the section "What happens if I'm in the interval training group?".
   d. Please move the text in the section "How hard do I have to take pedal?" to " What will happen to me if I take part"
   e. Please move the text in the section, "What is continuous exercise?" to "What happens if I'm in the continuous training group."
   f. On page 2, under the section "What will happen to me if I take part?", paragraph 2, line 3, please include details on the total volume of blood in mls and teaspoons and how the blood will be taken.
   g. On page 3, under the section, "Are there any disadvantages or risks of taking part? " Please add the text "All aerobic exercise carries some risk of injury be it a cardiovascular risk or a musculoskeletal injury and this can never be fully eliminated. However, the controlled environment and supervision of the CI throughout all training sessions will limit the risk greatly. The CI is a physiotherapist and will have immediate access, if needed, to medical staff that are aware of the study "similar to A12 and A22 of the REC form to describe the cardiovascular risks and associated mitigating factors. Also add a line about the potential risks in the form of discomfort with blood samples to be taken.

3. Consent form changes

   a. Please provide lay title similar to the one in the poster in addition to the full study title.
   b. In the header "Patient Identification Number for this study", please change 'patient' to 'participant'.
   c. Please add the minor typo 's' after 'researcher' in the header "Name of Researcher"

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites(if applicable)

The Committee has not yet completed any site-specific assessment(s) (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee thought that it was a worthwhile study and they felt that the rationale and design of the study seems appropriate.

The protocol mentions lipids profile but this is not covered in the IRAS form. The Committee asked if there was any reason why HDL was not measured.

Dr Coulter stated that they have only added what she had experience of and can add HDL if need be.

The Committee was satisfied with this.

The Committee asked who does the BDNF

Dr Coulter again advised that they have experience within the team.

The Committee asked for clarity around samples storage

You said that samples are stored, defrosted and analysed in batches.

The Committee was satisfied with this.

Recruitment arrangements and access to health information, and fair participant selection

The Committee noted that the participants attending the Douglas Grant rehabilitation centre in NHS Ayrshire and Arran and MS support groups within the same area will be given the PIS by a team member and they will contact the research team themselves or if they give permission the staff will contact the PI. The CI will then ask permission to contact GP GP's "consent". They were unsure what happens if the GP does not reply. They also wanted to know if the GP will give consent.The Committee were unhappy that the GP was being asked to assess patients suitability for the study and that this would be better done by the consultants looking after the MS Patients at the rehabilitation centre.

The Committee asked if the GP will be expected to consent and confirm that it is safe for the patient and if this is standard in Ayrshire and Arran.

Dr Coulter stated that this is done as an extra back up.

The Committee asked what the plan is if the GP is not responding.

Dr Coulter said that another letter will be sent but excluded if no GP consents.

The Committee stated that the onus is on the GP and the exclusion criteria are quite clear.

Dr Coulter stated that they are happy to take it out. She added that they could speak to the consultant if they are happy to do it as it should come from the secondary care. She added that consultant is also in the care/research team.

The Committee was satisfied with this

The Committee sought clarification with regards to the letter of invite as they were unsure how this will operate.

You stated that any member of the research team will hand it out with the PIS.

The Committee was satisfied with this.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee noted that although HIIT intuitively seems that it may be a potentially harmful but there is literature review that suggests that it is relatively safe. However, it was noted that the CI will be present to reduce risks significantly and this is not stated in the PIS.

The Committee asked if HIIT is safe

Dr Coulter said yes

The Committee asked if it is safe for this MS group

Dr Coulter said yes and added that it is done in various groups i.e. Parkinson's etc. She said that it has been done in MS but not progressive MS.

The Committee asked if there was specific risk for these groups i.e. falls and relapse and whether or not they will be able to do the study.

Dr Coulter said that it is based on their capabilities and there will be baseline. She added that they have seen it done in high level of disability elsewhere.

The Committee was satisfied with this

Informed consent process and the adequacy and completeness of participant information

The Committee had no issues with the informed consent process and thought that it is all appropriate. However, they had a comment with regards to the use of MOCA to assess capacity. They were unclear what will happen if the CI noted that. They thought that a score of <25 does not necessarily mean that it is an issue and felt that it should be taken out as some may be less than 25 but still have capacity.

The Committee asked about the MOCA and who administers it.

Dr Coulter stated that she does it.

The Committee asked if she has any training on this

Dr Coulter stated that she is not trained but if the score is less than 25 they will not take part and will inform GP.

The Committee added that cognitive impairment does not necessarily relate to capacity and required this taken out.

Dr Coulter confirmed that they are happy to take it out.

The Committee required written confirmation of this.

The Committee advised that of some minor changes required to the PIS.

Dr Coulter was happy with the proposed recommendations in to the PIS.

The Changes required to the PIS are detailed in the decisions above.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Awareness Poster]	1	01 November 2016
Covering letter on headed paper [Cover letter to REC]		15 November 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [UofG insurance evidence]		23 November 2016
GP/consultant information sheets or letters [GP letter]	1	01 November 2016
Letters of invitation to participant [Invitation letter]	1	15 November 2016
Other [Dr Elaine Coulter's CV]		
Other [Dr Paul Mattison's CV]		17 September 2013
Other [Borg scale of perceived exertion]	1	15 November 2016
Participant consent form [Consent form]	1	01 November 2016
Participant information sheet (PIS) [Participant information sheet]	1	01 November 2016
REC Application Form [REC_Form_09122016]		09 December 2016
Research protocol or project proposal [HIIT Protocol]	1	03 November 2016
Summary CV for Chief Investigator (CI) [Evan Campbell's CV]		
Summary CV for student [Evan Campbell's CV]	1	06 December 2016
Summary CV for supervisor (student research) [Dr Lorna Paul's CV]		09 November 2017
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flow chart of protocol]	1	06 December 2016
Validated questionnaire [HADS]	1	06 December 2016
Validated questionnaire [Montreal Cognitive Assessment]	1	06 December 2016
Validated questionnaire [MSIS-29]	1	06 December 2016
Validated questionnaire [Fatigue Scale of Motor and Cognitive functio]	1	06 December 2016
Validated questionnaire [Symbol Digit Modalities Test]	1	06 December 2016

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/WS/0005	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Abibat Ackwumi

On behalf of
Dr Brian Neilly
Chair

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Dr Karen Bell, NHS Ayrshire & Arran*

West of Scotland REC 4

Attendance at Committee meeting on 06 January 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Miss Lynda Brown	Public Health Adviser	Yes	
Ms Cristina Coelho	Senior Pharmacist Clinical Effectiveness	Yes	
Dr Michael Fail	Consultant Geriatrician	Yes	
Dr Kay Greenshields	Account Manager for Scottish Enterprise	Yes	
Dr Ken James	Consultant Anaesthetist	No	
Mrs Janet Johnstone	Research Nurse	No	
Dr Agata Kochman	Consultant Pathologist	Yes	
Dr Rachael MacIsaac	Stroke Trials Statistician	Yes	
Miss Fiona Mackelvie	Retired Administrator	No	
Mrs Karen McIntyre	Freelance Consultant	No	
Dr Brian Neilly	Consultant Physician	Yes	Chair of Meeting
Dr Giles Roditi	Consultant Radiologist	Yes	
Ms Aileen Scullion	Retired Head Teacher	Yes	
Mr John Woods	Retired Project Co-ordinator	Yes	
Mr Iain Wright	Retired - Technical Manager	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Abibat Adewumi-Ogunjobi	Acting REC Manager (Minute taker)
Miss Sophie Bagnall	Assistant Coordinator
Wendy Cohen	Observer
Dr Judith Godden	Scientific Adviser
Ms Rozanne Suarez	REC Manager (New staff as part of training)

Written comments received from:

Name	*Position*
Mrs Karen McIntyre	Freelance Consultant

Appendix 7 – Research and development approval letter

Research & Development Office
58 Lister Street
Crosshouse Hospital
Kilmarnock
KA2 0BB

Mr Evan Campbell
University of Glasgow
59 Oakfield Avenue
Glasgow
G12 8LL

Date 10 February 2017
Your Ref
Our Ref AG/KLB/AMK 2016AA090

Enquiries to Karen Bell
Extension 25850
Direct line 01563 825850
Fax 01563 825806
Email Karen.bell@aaaht.scot.nhs.uk

Dear Mr Campbell

Letter of access for research

The effect of High Intensity Interval Training on cardiovascular fitness in people with progressive Multiple Sclerosis.

This letter confirms your right of access to conduct research through NHS Ayrshire & Arran for the purpose and on the terms and conditions set out below. This right of access commences on **10 February 2017** and ends on **31 January 2018** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at NHS Ayrshire & Arran has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to NHS Ayrshire & Arran premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through NHS Ayrshire & Arran you will remain accountable to your employer **University of Glasgow** but you are required to follow the reasonable instructions of **Linda Renfrew** in this NHS organisation or those given on her behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with NHS Ayrshire & Arran policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with NHS Ayrshire & Arran in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on NHS Ayrshire & Arran premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Where required by law, your HEI employer will initiate your Independent Safeguarding Authority (ISA) registration, and thereafter, will continue to monitor your ISA registration status via the on-line ISA service. Should you cease to be ISA-registered, this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity. You MUST stop undertaking any regulated activity.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

NHS Ayrshire & Arran will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Dr Alison Graham
Medical Director

c.c. Peter Blyth, HR department of University of Glasgow
Linda Renfrew, NHS Ayrshire & Arran

www.nhsaaa.net

Appendix 8 – Poster to raised awareness for exercise trial

Exercise training for people with progressive Multiple Sclerosis

NHS Ayrshire & Arran

We are looking for people who have progressive MS to take part in a research study, comparing two types of exercise training on an exercise bike.

Ask your health care practitioner at the Douglas Grant if you are interested in taking part

Or for further information, contact

Linda Renfrew or Evan Campbell

Tel: 01294 323 057/ 0141 330 7154

University of Glasgow

Appendix 9 – Participant information sheet

Participant information sheet
Exercise training for people with progressive Multiple Sclerosis
Improving fitness in people with progressive Multiple Sclerosis using either continuous or interval exercise.

This study is being carried out by the University of Glasgow and NHS Ayrshire & Arran. Before you decide whether or not you wish to take part is important that you understand what the study will involve and why we are doing the research. Please read the following carefully and if you have any questions please do not hesitate to ask us if something is not clear.

What is the purpose of the study?

We are carrying out this study to see if we can improve fitness of people with progressive Multiple Sclerosis (MS). We will do this by using high intensity interval training (described below) on an exercise bike, twice a week, for eight weeks. We will then compare these results to the results of people who have undertaken a similar exercise programme but at lower exercise intensity and without breaks.

Why is this important?

Having poor fitness is linked to risk factors for many diseases such as heart disease and diabetes. Previous research has shown that people with MS have poorer fitness than those without MS. This puts people with MS at a higher risk of developing these diseases.

Why have I been chosen?

You have been chosen because you are a person with progressive Multiple Sclerosis and are able to pedal on an exercise bike.

Do I have to take part?

No, it is entirely up to you whether or not you choose to take part. Also if you start and then decide that you don't want to continue you are free to stop at any point.

What will happen to me if I take part?

If you choose to take part we will send a letter to your GP to tell them that you are taking part. You will then be invited to attend Douglas Grant Rehabilitation Centre in Irvine. Once there we will explain the study in detail and then take your blood

pressure and ask you some questions about your past medical history to make sure that it is suitable and safe for you to take part.
If you are suitable to take part in the study we will then do the heart rate test that was described above, ask you to fill out some questionnaires, measure your walking speed and take some blood samples. We will take blood from a vein in your arm we will only take 10 mls (2 teaspoons) of blood. The blood samples are to examine the levels of a hormone which is important in brain health, your cholesterol, and how much exercise waste materials (lactate) you have in your blood.
At this point you will be asked to pick an envelope. Inside will be a piece of paper which will tell you if you are in the interval training group or the continuous training group.

What happens if I'm in the interval training group?

Interval training means short bursts of high effort followed by short periods of low effort. In our interval training program you will spend a total 20 minutes on an exercise bike. After a 2 minute warm up you will pedal hard for 90 seconds and then pedal lightly for 90 seconds. The hard pedalling followed by light pedalling will be repeated another 5 times. After this you will then have a 3 minute cool down. This means that over the 23 minutes you only do a total of 9 minutes hard work!
In the week before the start of the study we will ask you to attend an appointment with us. At this appointment you will cycle as hard as you can on the exercise bike and we will monitor how high your heart rate goes. This will take about 10 minutes. We will use your highest heart rate to calculate a target heart rate for the hard pedalling intervals during the study. We will repeat this test again after the study has finished to see if your highest heart rate has changed.
If you are in the intervention group you will do the interval training programme. This means that you will attend the Douglas Grant rehabilitation Centre twice a week for 8 weeks. Each appointment will last approximately 1 hour. Even though the training only takes 23 minutes you will rest afterwards. It is common for your legs to be tired and to have a temporary increase in your leg symptoms but these will usually pass within 30 minutes.
At the end of the study we will ask you attend one more time to do the same heart rate test, questionnaires that we did before you started and take some more blood.

What happens if I'm in the continuous training group?

Continuous exercise means exercising at a constant intensity for a set period of time. In our continuous training program you will spend a total of 35 minutes on the exercise bike. After a 2 minute warm up you will pedal at a medium intensity for 30 minutes and then have a 3 minute cool down.
If you are in the continuous training group you will do the continuous exercise program. This means that you will attend the Douglas Grant rehabilitation Centre twice a week for 8 weeks. Each appointment will last approximately 1 hour to allow time for you to rest afterwards.
At the end of the study we will ask you attend one more time to complete the same heart rate test, questionnaires that we did before you started and take some more blood samples.

Are there any disadvantages or risks of taking part?

All exercise carries some risk of injury and this can never be fully eliminated. However, during this trial you will be exercising in a controlled environment and a physiotherapist will be with you at all times. There will also be medical staff on hand if they are ever needed.
After doing strenuous leg exercise it is common for people with MS to feel an increase in their leg symptoms (such as pins and needles) but these usually pass quickly and resolve in about 30 minutes. In addition it is common for everybody who exercises to feel little muscle soreness and tiredness both during and after they exercise. This is also normal and temporary. However, there will always be a physiotherapist and their assistant present throughout all of your training who will make sure you are safe.
You may feel some discomfort when the blood samples are being taken. This will be similar to receiving an injection at the doctor's.

What are the possible benefits of taking part?

You may find that after completing the exercise programme (both the interval and continuous training groups) that your fitness improves. This means that your heart and lungs are working more efficiently. You may also find that your leg muscles become stronger and have more stamina. You will also find out about your measurements such as blood pressure and how these have changed over the 8 weeks.

Will I have to pay for my travel?

No, we will cover you travel expenses for all of your visits to Douglas Grant Rehabilitation Centre. Just make sure you keep your receipts for any taxi or bus journeys and we can reimburse you.

What happens when the research study stops?

When the study stops we will give you a summary of all of your individual measurements as well as a summary of the findings of the study.

Will my taking part in this study be kept confidential?

Yes. All of your details will be made anonymous. If any of your measurements are used for publications or presentations there will be no information displayed that could identify you.

What happens if new information becomes available?

If new information becomes available we will discuss this with you.

What will happen if I don't want to continue in the study?

If you want to stop taking part in the study this is fine. You are free to stop at any point.

What happens to the results of the research study?

The results will be used as part of Evan Campbell's PhD and may also be used to write an article for a medical journal.

Who is organising and funding the study?

The study has been organised by the academic staff from the University of Glasgow. The study is funded by the Bevan Scholarship which is funding Evan Campbell's PhD and came from NHS Ayrshire & Arran.

Who has reviewed this study?

This study has been reviewed and approved by the West of Scotland Research Ethics Service.

Participation, further information and contact details.

If you are interested in taking part, have any questions about whether or not you should take part in the study please contact:

Evan Campbell
University of Glasgow
Tel: 0141 330 7154
Email: e.campbell.4@research.gla.ac.uk.

Alternatively if you would like to talk to someone who has an understanding of the research but is not directly involved in the study please contact:
Dr Aleksandra Dybus
University of Glasgow
Tel: 0141 330 5536.

Thank you for taking the time to read this information sheet

Exercise training for people with progressive Multiple Sclerosis

Improving fitness in people with progressive Multiple Sclerosis using either continuous or interval exercise.

I _____ give my consent for my contact details to be given to Evan Campbell so they can contact me about participation in the above study.

Signed: _____

(Participant copy)

(Please cut/tear along line)

Exercise training for people with progressive Multiple Sclerosis

Improving fitness in people with progressive Multiple Sclerosis using either continuous or interval exercise.

I _____ give my consent for my contact details to be given to Evan Campbell so he can contact me about participation in the above study.

Signed: _____

(Researcher's copy, please give to Evan Campbell)

Appendix 10 – Consent form

Participant Identification Number for this study: ☐

STUDY CONSENT FORM

Title of Project: The effect of high intensity interval training on cardiovascular fitness in people with progressive Multiple Sclerosis.

Lay title: Exercise training for people with progressive Multiple Sclerosis

Name of Researchers: Mr Evan Campbell, Dr Lorna Paul, Dr Elaine Coulter

Please initial boxes

1. I confirm that I have read and understand the participant information sheet (ver 2 dated 20/01/2017) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. All data (personalised and study data) collected up to the point of withdrawal from the study will be retained until the end of the study. ☐

3. I understand that information collected about me may be looked at by authorised individuals from the study sponsor, NHS Ayrshire & Arran or from the regulatory authorities to ensure that the study has been performed to the appropriate standards. ☐

3. I give permission for the researchers to contact my GP to inform them of my participation. ☐

4. I agree to my GP will be informed of any abnormal results that may arise during assessment or screening. ☐

5. I give permission for my blood sample to be stored at The University of Glasgow until the end of the study. ☐

7. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Researcher	Date	Signature

*1 copy for participant , 1 copy for researcher and 1 copy for participant's notes

Appendix 11 – Letter to general practitioner

Date:

Re:

Dear Doctor

Re: Improving fitness in people with progressive Multiple Sclerosis using either continuous or interval exercise.

I am writing to inform you that the patient named above has expressed interest in taking part in this study which is being conducted by staff at the University of Glasgow and is funded by NHS Ayrshire & Arran. The study has two groups and the patient will be randomly allocated to the either receive an interval training program or a continuous training program (both described below).

The overall aims are to increase fitness in people with progressive MS using high intensity interval training and compare this to continuous training at a moderate intensity. People with MS are at a higher risk of developing cardiovascular co-morbidities and this is partly due to the decreased fitness seen in this population. We hope by participating in this study that the participants will increase their fitness and thus decrease their risk factors of developing such co-morbidities. Both training programs will be on an exercise bike, twice weekly for 8 weeks and will be carried out in the Douglas Grant Rehabilitation Centre, Ayrshire Central Hospital.

The interval training group will perform 6x 90 second exercise bouts at 80-95% of their heart rate max interspersed with 90 second intervals of active rest to bring their heart rate down to 60-70% of heart rate max. After the last working rest there will be a 3 minute cool down. The continuous training group will cycle for 30 minutes at 60-70% of their heart rate max and then have a 3 minute cool down. After the cool down participants in both groups will be given the opportunity to rest for up to one hour.

I have attached a patient information sheet for your information. If you require any further information or have any questions please do not hesitate to contact me.

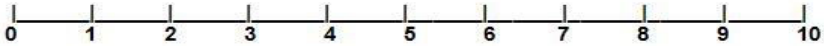
Yours sincerely,

Evan Campbell
Research Physiotherapist and PhD Candidate
School of Medicine
The University of Glasgow
59 Oakfield Avenue
Glasgow
G12 8LL Tel: 0141 330 7154 email: e.campbell.4@research.gla.ac.uk

Appendix 12 – Symptom diary

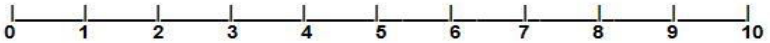
Symptom Diary

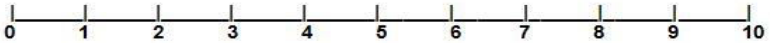
Please rate all of your symptoms on the following scale out of 10. 10 is the worst and 0 is the best.

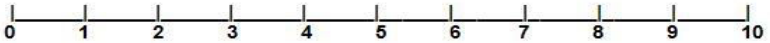


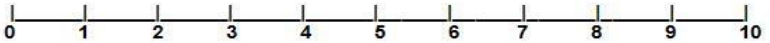
No symptom **Worst symptom**

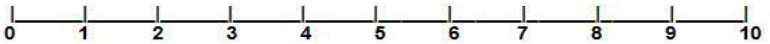
Answer **before** your training session. How is your

Fatigue 

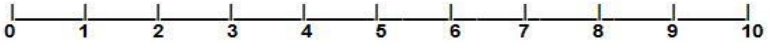
Pain 

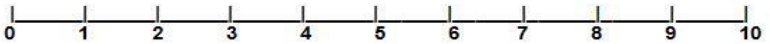
Spasms 

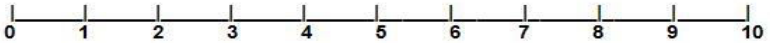
Pins and needles/ numbness 

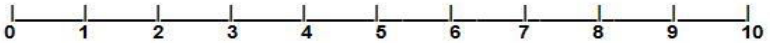
Other _____ 

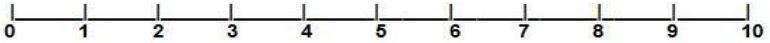
In the **afternoon of** _____ how was your (**do not answer if your training session was in the afternoon**)

Fatigue 

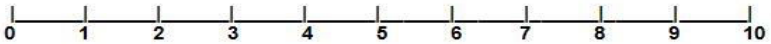
Pain 

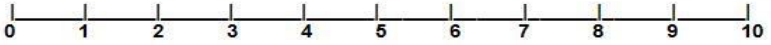
Spasms 

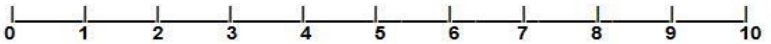
Pins and needles/ numbness 

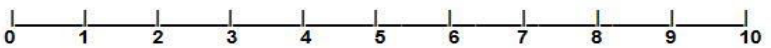
Other _____ 

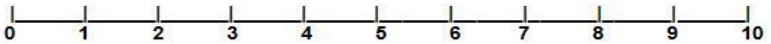
In the **evening of** _____ how was your

Fatigue 

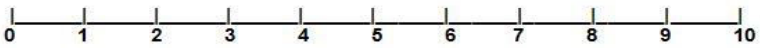
Pain 

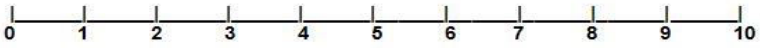
Spasms 

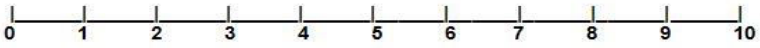
Pins and needles/ numbness 

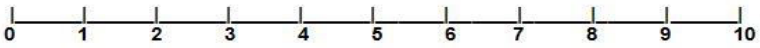
Other _____ 

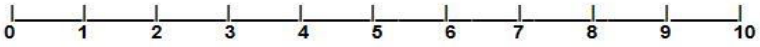
In the **morning of** _____ how was your

Fatigue 

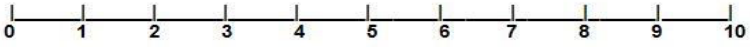
Pain 

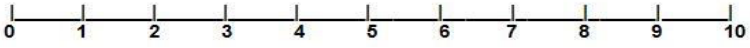
Spasms 

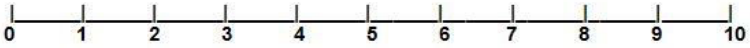
Pins and needles/ numbness 

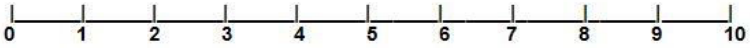
Other _____ 

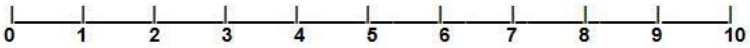
In the **afternoon of** _____ how was your

Fatigue 

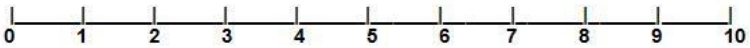
Pain 

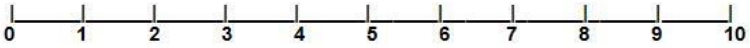
Spasms 

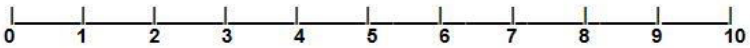
Pins and needles/ numbness 

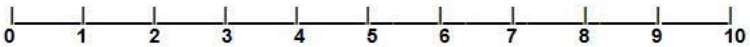
Other _____ 

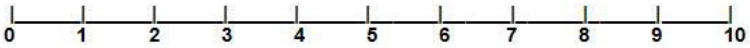
In the **evening of** _____ how was your

Fatigue 

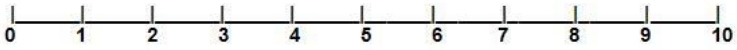
Pain 

Spasms 

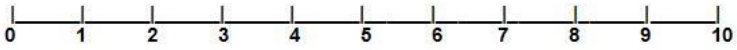
Pins and needles/ numbness 

Other _____ 

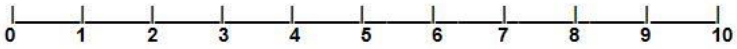
In the **morning of** _____ how was your
Fatigue



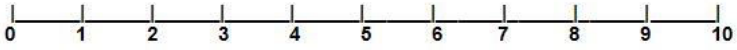
Pain



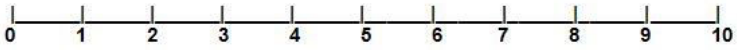
Spasms



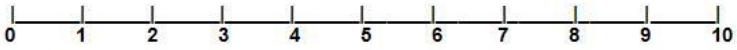
Pins and needles/ numbness



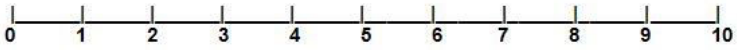
Other _____



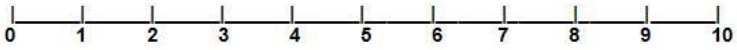
In the **afternoon of** _____ how was your
Fatigue



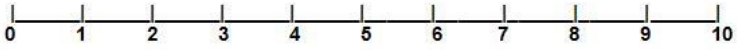
Pain



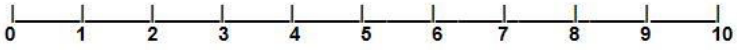
Spasms



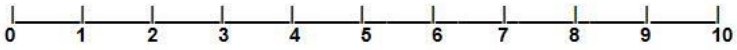
Pins and needles/ numbness



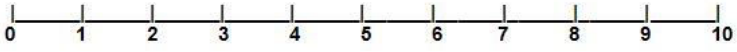
Other _____



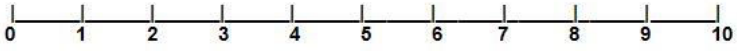
In the **evening of** _____ how was your
Fatigue



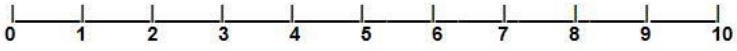
Pain



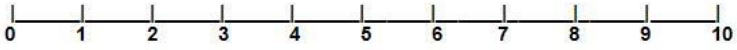
Spasms



Pins and needles/ numbness



Other _____



Appendix 13 – Symbol Digit Modalities Test

≥	±	«	∏	ж	ψ	Δ	o	↑
1	2	3	4	5	6	7	8	9

ψ	±	∏	ψ	±	o	≥	Δ	↑	ж	±	«	±	≥	Δ
6	2	4												

ж	Δ	↑	o	∏	«	Δ	↑	ж	±	«	«	«	ж	ψ

o	±	«	∏	ж	ψ	≥	o	±	≥	±	«	«	ψ	o

≥	∏	«	ψ	ж	±	Δ	o	↑	o	±	«	∏	ж	«

±	±	«	∏	ж	ψ	o	±	o	≥	±	«	∏	o	ψ

«	∏	«	Δ	«	∏	Δ	o	↑	Δ	«	«	Δ	ж	ψ

≥	±	«	±	ж	«	±	o	«	≥	±	±	∏	Δ	ψ

Appendix 14 – 10 point Borg scale of perceived exertion

0	Nothing at all
0.5	Very, very slightly (just noticeable)
1	very slightly
2	Slight (light)
3	moderate
4	Somewhat strong
5	Strong (heavy)
6	
7	Very Strong
8	
9	
10	Very, very strong (maximal)

Appendix 15 – Baseline data from five participants who restarted exercise trial

Participant	7		8		9		10		11		
	B1	B2	B1	B2	B1	B2	B1	B2	B1	B2	*p*
Weight (kg)	80.7	79.5	96.3	97	94.1	95.2	77.2	77.1	58.3	59.4	0.506
Resting HR (bpm)	75	66	62	59	74	82	91	93	65	75	0.671
Systolic BP (mm/Hg)	149	108	124	123	158	128	119	125	130	126	0.199
Diastolic BP (mm/Hg)	66	64	83	80	99	97	70	76	70	74	0.760
T25FW (s)	8.1	8.7	5.2	5.3	7.2	7	23.3	23.5	5.5	6.2	0.166
MSIS- 29 Phys	47	53	48	50	48	48	60	51	45	45	0.939
MSIS-29 Psych	17	17	22	19	13	11	31	34	24	25	0.861
HADS Anx	2	6	11	8	3	3	3	3	11	12	0.740
HADS Dep	4	5	8	0	6	5	9	5	8	10	0.333
FSMC Total	87	87	75	83	59	50	93	92	71	61	0.507
FSMC Motor	45	45	39	42	33	26	49	48	37	33	0.353
FSMC Cog	42	42	36	41	26	24	44	44	34	28	0.753
SDMT	33	34	28	28	47	43	14	15	41	48	0.600
Resting Lact (mmol/l)	1.0	5.4	0.5	1	2.8	1.5	3.9	2.5	5.3	1.7	0.845
HRMax (bpm)	148	135	132	137	146	138	111	124	148	137	0.608
Peak Lact (mmol/l)	12.0	11.6	6.6	15.5	12	12.4	3.6	4.3	6.1	4.4	0.447

Abbreviations: HR: heart rate; BP: blood pressure; T25FW: timed 25 foot walk test; MSIS-29: multiple sclerosis impact scale; Phys: physical sub-scale; Psych: psychological sub-scale; HADS: hospital anxiety and depression scale; Anx: anxiety; Dep: depression; FSMC: fatigue scale for motor and cognitive function; Mot: motor; Cog: cognitive; SDMT: symbol digit modalities test; lact: lactate; HRMax; maximal heart rate; B1: first baseline measurement; B2: second baseline measurement

All testing paired sampled t tests.